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CHAPTER 1

Diagnosis and Epidemiology of ARDS

Review by Nicholas S. Hill

Acute respiratory distress syndrome (ARDS) is a disease of modern technology. Without oxygen supplementation and mechanical ventilation as well as modern diagnostic technology, patients with incipient respiratory failure cannot survive long enough to show more than the initial features of ARDS let alone have the diagnosis made. It is not an accident that Ashbaugh and Petty described the syndrome during the 1960s as ICUs and blood gas machines were becoming available, and they also launching their academic careers.

ARDS clearly antedated its description. Mendelsohn's syndrome was an example, described during the late 1940s in women who developed often lethal severe hypoxic respiratory failure after gastric aspiration that occurred as they were being intubated during labor, a common practice at that time. The reports of Da Nang Lung on massive trauma victims during the Vietnam War was another.

The dozen patients described by Ashbaugh and Petty in their *Lancet* 1967 report exemplified the typical findings of the syndrome: acute onset of severe dyspnea, cyanosis, and bilateral patchy infiltrates on chest x-ray. Patients responded poorly to oxygen supplementation unless given positive end-expiratory pressure (PEEP), and lung compliance was low. Pathology revealed diffuse alveolar damage and hyaline membranes. Some patients seemed to respond to corticosteroids, but mortality was still very high at 75%.

In the years since the syndrome was described, the epidemiology of ARDS has been very controversial with estimates of incidence varying from 3.5/100,000/yr on one of the Canary Islands to 58.7/100,000/yr for the Seattle area. On average, the incidence in the US has been much higher than in Europe, sometimes by an order of magnitude. Possible reasons for these disparities are manifold but include the use of different definitions that have been evolving over time: under and over-reporting, different populations with different risk factors, and health practices in different regions, hospitals, and even ICUs within the same hospital. Some of the more notable studies include the one done near Seattle, which came up with an incidence of 58.7/100,000/yr and used careful screening and quality control to avoid missing patients. The COVID-19 pandemic will undoubtedly affect the incidence of ARDS for the years 2020 and 2021, but it is too early for the cases to have been counted yet.

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A number of risk factors are well known to affect the likelihood of developing ARDS as well as outcomes. These include age, which in the Kings County, Washington, study (near Seattle) showed that patients >85 were almost 200 times more likely to have ARDS than those in their late teens. Other important risk factors for ARDS and mortality include immunodeficiency and multi-organ deficiency.

As a syndrome, ARDS is associated with no one etiology or mechanism of injury. Instead, there are dozens that have been identified, lumped broadly into pulmonary (or direct) and extra-pulmonary (or indirect) categories. The former includes pneumonia, aspiration pneumonitis, toxin inhalation, and near drowning as a few examples, whereas the latter includes sepsis, severe trauma, pancreatitis, and massive transfusion, and carries a worse prognosis because it is more often associated with multi-organ system dysfunction.

Mortality of ARDS has been less controversial than the incidence of ARDS. Earlier studies showed mortalities exceeding 50%, ranging up to 70%. Since the 1990s, overall mortality has been in the 40% range. The ALIEN study from Spain was disappointing in that the overall hospital mortality rate was nearly 48% despite the implementation of lung-protective ventilator strategies over the previous decade. The more recent LUNG SAFE trial has also shown overall hospital mortality rates in the 40% range for moderate and severe ARDS, corresponding to the ARDS category in the American European Consensus Conference (AECC) definition of ARDS, and was also disappointing in this regard. This may be related to the fact that mortality of ARDS is less often related to the respiratory failure than to other organ failures.

The LUNG SAFE study used a computer algorithm to screen for ARDS according to the Berlin definition, and the rate of clinician recognition was determined by if they included it as a potential diagnosis in their notes. Recognition was only roughly 50% in mild ARDS but nearly 89% in severe ARDS. Lack of recognition was associated with fewer interventions that have been shown to be associated with better outcomes in ARDS such as lung-protective ventilator strategies, higher levels of PEEP, and using the prone position.

Splitters often consider ARDS a “wastebasket” diagnosis which lumps too many different etiologies into the same bucket. This has complicated making sense of the epidemiology because ARDS in one study may not be defined and detected in the same way as the next. It also complicates clinical trials because of the heterogeneity of the populations enrolled. On the other hand, it has been useful for the study of therapies that address the common pulmonary pathophysiology such as using low tidal volumes or the prone position. In the not too distant future, using precision medicine, it may be possible to better delineate different mechanisms of ARDS, which should refine the classification and pave the way for trials of better targeted therapies.

ANNOTATED REFERENCES FOR DIAGNOSIS AND EPIDEMIOLOGY OF ARDS

ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526–2533.

Consensus conference to update the AECC definition that took place in Berlin. The participants reclassified the ALI category with PaO_2/FIO_2 ratio <300 and ≥200 as mild ARDS, PaO_2/FIO_2 <200 and ≥100 as moderate ARDS and PaO_2/FIO_2 <100 as severe. Minimum PEEP for assessing PaO_2/FIO_2 was 5 cm H_2O. Other aspects of the AECC definition were retained; acute onset, but defined as within one week, bilateral infiltrates on chest x-ray but not explained by effusions, atelectasis, or nodules, and respiratory failure not fully explained by cardiac failure or fluid overload (and no need for pulmonary artery catheterization to prove it). Four ancillary physiologic variables were considered; severity of chest x-ray abnormalities, compliance ≤40 mL/cm H_2O, PEEP ≥10 cm H_2O and minute volume ≥10 L/min, but these did not improve prediction of outcome when evaluated in a clinical dataset and were dropped.

Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967;2:319–323.

First description of ARDS in 12 patients with acute hypoxic respiratory failure when the authors were just starting their faculty careers. They noted that "The clinical pattern … includes severe dyspnoea, tachypnoea, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and a diffuse alveolar infiltrate seen on chest X-ray." They describe and recommend the use of PEEP to improve oxygenation.

Bellani G, Laffey JG, Pham T, et al. LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788–800.

Using the LUNG SAFE (Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE) database from 459 ICUs in 50 countries worldwide. Of 29,144 patients admitted to the ICUs, 10.4% met the Berlin criteria for ARDS and 23.4% of the patients were on mechanical ventilation. Thirty percent of ARDS cases were mild, 46.6% moderate and 23.4% severe. Hospital mortality was 34.9% in mild, 40.3% in moderate, and 46.1% in severe cases. Recognition of ARDS was only 51.3% in mild cases up to 78.5% in severe. Failure to recognize ARDS was associated with underutilization of lung protective ventilator strategies, lower levels of PEEP, and less use of the prone position or neuromuscular blockade.

Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149:818–824.

Consensus conference convened to address problems with inconsistencies in definition of ARDS that was leading to difficulties in determining the epidemiology of ARDS. This group established the previous definition of acute lung injury (ALI) and ARDS as conditions characterized by acute onset, bilateral infiltrates on CXR, and pulmonary artery wedge pressure (PAWP) ≤18 mm Hg or no clinical evidence of left atrial hypertension. The two were distinguished by PaO_2/FIO_2 ratio ≤300 for ALI and ≤200 for ARDS.

Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med.* 2004;30(1):51–61.

The study identified 463 patients (7.1% of ICU admissions) with ALI (16.1% of mechanically ventilated patients). Sixty-two patients (13.4%) remained with mild ALI; the remainder had ARDS. Mortality of mild ALI was 32.7% and of ARDS was 57.9%. Risk factors for mortality included greater age, immunodeficiency, multiple organ dysfunction, and pH <7.30.

Luhr OR, Antonsen K, Karlsson M, et al., and the ARF Study Group. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. *Am J Respir Crit Care Med.* 1999;159:1849–1861.

Eight-week cohort study of 132 ICUs in Sweden, Denmark, and Iceland, using American European Consensus Conference (AECC) definitions. They found an incidence and hospital mortality of 77.9/100,000/yr and 42.2% for acute respiratory failure (ARF) including acute lung injury (ALI), 17.9/100,000/yr and 42.2% for ALI including ARDS and 13.5/100,000/yr and 41.2% for ARDS, respectively. This heralded a reduction in ARDS mortality that some doubted at the time but seems to have held up.

Murray JF, Matthay MA, Luce JM, Flick MR. Expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988;138:720–723.

Description of the Murray Lung Injury Score incorporating ratings of severities of chest x-ray, PaO_2/FIO_2, PEEP, and compliance abnormalities. The score lost favor because of a lack of correlation with outcomes.

Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med.* 2005;353:1685–1693.

Identified 1113 patients in Kings County Washington, US, receiving mechanical ventilation who met AECC criteria for ALI. Found overall incidence of 78.9/100,000/yr for ALI and 58.7/100,000/yr for ARDS. Incidence varied with age from 16/100,000/year for ages 15–19 years to 306/100,000/yr for ages 75–85 yrs. Overall mortality was 38.5%, varying from 24% for ages 15–19 to 60% for age >85 yrs. The authors had a meticulous protocol for screening patients to enhance confidence in their numbers.

Villar J, Slutsky AR. The incidence of the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1989;140:814–816.

Study done on the island of Las Palmas on the Canary Islands over a 3-year period. Using a definition of $PaO_2 \leq 75$ mm Hg on $FIO_2 \geq 0.5$, they estimated an incidence for ARDS of 3.5/100,000/yr. This illustrates the range of reported incidences related to differing definitions in the past.

Villar J, Blanco J, Añón JM, et al. The ALIEN (Acute Lung Injury: Epidemiology and Natural history) study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med.* 2011;37:1932–1941.

Prospective multicenter study of ICUs in 13 geographic regions of Spain. Two-hundred-fifty-five consecutive patients that met AECC criteria for ARDS were enrolled. Overall incidence of ARDS was 7.2/100,000/yr and hospital mortality was 47.8%. Average PaO_2/FIO_2 ratio was 114, tidal volume was 7.2 mL/kg, plateau pressure was 26 cm H_2O and PEEP was 9.3 cm H_2O. The authors speculated on possible reasons for the much higher incidences of ARDS reported from US studies compared to European ones. The authors also remarked that ARDS mortality was stable over the previous 10 years despite implementation of lung protective ventilator strategies.

Landmark Article of the 21st Century

EPIDEMIOLOGY, PATTERNS OF CARE, AND MORTALITY FOR PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME IN INTENSIVE CARE UNITS IN 50 COUNTRIES

Bellani G et al., *JAMA*. 2016;315(8):788–800

Commentary by John G. Laffey

In 2012, the Berlin definition for ARDS was developed, which heralded significant changes in how ARDS was diagnosed. I had recently taken on the role of deputy chair of the Acute Respiratory Failure section of the European Society of Intensive Care Medicine (ESICM), and together with Prof. Antonio Pesenti, the section chair, we decided to conduct a prospective cohort study to "validate" the definition and understand the "real world" management and outcomes of ARDS in the 21st century.

With relatively little direct funds, other than "in kind" support from the ESICM, St Michael's Hospital Toronto (my then institution), and University of Milan-Bicocca (A. Pesenti's and G. Bellani's institution) we engaged with the ESICM research community to enroll sites into "LUNG SAFE" as we called the study. We were astonished at the response, over 660 centers from over 50 countries on all continents indicated that they would participate. We opened the study for 3-month enrollment windows in the winter periods of both the Northern and Southern hemispheres in 2014. We asked centers to enroll for a 4-consecutive-week period. In all, we collected data on over 29,000 patients from 636 hospitals (666 ICUs) of whom over 12,000 were included in the analysis, of whom 4499 had acute hypoxemic respiratory failure, and just over 3000 of whom fulfilled the Berlin criteria for ARDS.

This primary paper described the cohort of 2377 patients that developed ARDS within 48 hours of ICU admission and required invasive mechanical ventilation. An important aspect of the design is that we didn't ask physicians to decide whether a patient had ARDS—we collected sufficient data to enable independent determination of the diagnosis. That resulted in three important findings: first, ARDS was greatly under-recognized, with only 34% recognized on day 1; second, ARDS prevalence was up to five times more frequent than previously estimated; and third, there was much less geographic variation in ARDS incidence than previously thought. ARDS accounted for 10% of all ICU admissions and 23% of patients requiring mechanical ventilation. Key evidence-based aspects of ARDS management were underused. One-third of patients with ARDS received a tidal volume over 8 of mL/kg predicted body weight, PEEP levels used were lower than expected, while prone positioning was used in a small minority of patients with severe ARDS. Clinician recognition of ARDS was associated with higher PEEP use, greater use of neuromuscular blockade, and prone positioning. Hospital mortality was 40% for all patients with ARDS.

Since this paper was published, over 25 subsequent papers have been published from the LUNG SAFE dataset, underlining the treasure trove of data therein, and giving a comprehensive picture of ARDS in the 21st century. **n = 438**

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Ards Treatment

Ashbaugh DG , Bigelow DB , Petty TL , Levine BE. Acute respiratory distress in adults. *Lancet* . 1967;290(7511):23–319.

Although the respiratory distress syndrome had been known to occur in soldiers during war (e.g., Da Nang Lung), this paper was the first description of the respiratory distress syndrome in adult civilians. Application of PEEP improved atelectasis and hypoxemia.

The ARDS Definition Task Force . Acute respiratory distress syndrome: the Berlin definition. *JAMA.* 2012;307(23):2526–2533.

The task force proposed mutually exclusive categories to characterize the severity of ARDS: mild (200 mm Hg < PaO2/FiO2 ≤300 mm Hg); moderate (100 mm Hg < PaO2/FiO2 ≤200 mm Hg); and severe (≤100 mm Hg). When analyzed against data sets from four clinical trials, these categories (mild to moderate to severe) were associated with an increase in mortality and median duration of mechanical ventilation in survivors.

Dreyfuss D , Soler P , Basset G , Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis.* 2012;137(5):1159064.

In a rodent model, the researchers prove convincingly that high tidal volumes rather than high pressure cause lung during mechanical ventilation.

Amato MB , Barbas CS , Medeiros DM , et al. Beneficial effects of the “open lung approach” with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. *Am J Resp Crit Care Med.* 1995;152:1835–1846.

In a small randomizes trial (n = 28), the authors compared the use of a tidal volume of <6 mL/kg, PEEP applied according to the lower inflection point of the total respiratory compliance curve, and peak pressures <40 cm H2O to a conventional approach of a tidal volume of 12 mL/kg and application of PEEP dictated by the FiO2 and hemodynamics. PaO2/FiO2 ratios and compliance were higher in the lower tidal volume group.

Ranieri VM , Suter PM , Tortorella C , et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1999;282:54–61.

Patients (n = 37) with ARDS were randomized to a control group or a lung protection strategy group (lower tidal volume and plateau pressure and high levels of PEEP). High levels of inflammatory mediators were found in the plasma and BAL of patients in the control group. A follow-up study also found a higher incidence of organ dysfunction in the control group.

Stewart TE , Meade MO , Cook DJ , et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *New Engl J Med*. 1998;338:355–361.

Patients (n = 120) at high risk for developing ARDS were randomized to either a tidal volume of ≤8 mL/kg and peak inspiratory pressures of ≤30 cm of H2O or tidal volumes of 10–15 mL/kg and peak inspiratory pressures of ≤50 cm H2O. There was no difference in mortality nor in episodes of organ failure. Hypercarbia and need for paralytics and renal replacement therapy was greater in the low tidal volume group.

The Acute Respiratory Distress Syndrome Network . Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301–1308.

Patients with ARDS were randomized to tidal volumes and plateau pressures of 6 mL/kg IBW and 30 cm H2O and 12 mL/kg IBW, respectively. Mortality was significantly lower in the group treated with a VT of 6 mL/kg. In addition, days free of mechanical ventilation were greater in this group.

Needham DM , Colantuoni E , Mendez-Tellez PA , et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *Br Med J*. 2012;344:e2124.

Consecutive patients (n = 485) from 13 hospitals with acute lung injury were followed for two years. After adjusting for relevant covariates, adherence to a lung protection strategy significantly improved two-year survival.

Guerin C , Reignier J , Richard J-C , et al. Prone positioning in acute respiratory distress syndrome. *New Engl J Med*. 2013;368:2159–2168.

Patients with severe ARDS (P/F <150) were randomized to either the prone or supine position. Patients in the prone group had an average of four sessions, each lasting approximately 17 hours. Both 28-day and 90-day mortality were significantly lower in the prone group. Cardiac arrest was more common in the supine group.

Papzian L , Forel J-M , Gacouin A , et al. Neuromuscular blockers in early acute respiratory distress syndrome. *New Engl J Med*. 2010;363:1107–1116.

Patients with early ARDS were randomized to a 48-hour duration of treatment with cis-atracurium or placebo. Neuromuscular monitoring was not performed to maintain blinding. Although the crude 90-day mortality was no different between groups, the 90-day mortality rate adjusted for the P/F ratio, SOFA score, and plateau pressure, was significantly lower in the cis-atracurium group. There was no difference in ICU-acquired paresis. Curiously, the separation of the two groups in the survival curve did not start to manifest itself until around day 20.

Petrucci N , De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Sys Rev*. 2013;(2):CD003844.

This third update of the use of lung protection strategy in treating ARDS patients shows that hospital and 28-day mortality is significantly reduced compared to the use of larger tidal volumes. Clinical heterogeneity was present based on different time lengths of follow-up and higher plateau pressures in the control groups.

Amato MBP , Meade MO , Slutsky AS , et al., Driving pressure and survival in the acute respiratory distress syndrome. *New Engl J Med*. 2015;372:747–755.

Using multilever mediation analysis, the authors analyzed data from nine randomized trials of mechanical ventilation in patients with ARDS. Driving pressure (plateau pressure – PEEP) was the variable that best stratified risk of mortality (the higher the driving pressure, the higher the risk).

Weaning from Mechanical Ventilation

Kurek CK , Cohen IL , Lamrinos J , Minatoya K , Booth FV , Chalfin DB. Clinical and economic outcome of patients undergoing tracheostomy for prolonged mechanical ventilation in New York State during 1993; analysis of 6,353 cases under diagnostic related group 483. *Crit Care Med*. 1997;25:983–988.

The overall survival rate of patients who undergo tracheotomy for prolonged mechanical ventilation was 49%. Survival was inversely correlated with age. Of the survivors, 21.6% were discharged to a residential healthcare facility, but that number was also significantly affected by age, with 68.5% of the oldest cohort (>90 years of age) requiring residential placement.

Unroe M , Kahn JM , Carson SS , et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation. A cohort study. *Ann Intern Med*. 2010;153:167–175.

Patients who undergo prolonged mechanical ventilation have a difficult course, often with readmission to the hospital and with multiple transitions in their care locations. Sixty-five percent of patients had a 1-year outcome of either complete functional dependency or death. The cost per year of independent function was estimated to be $3.5 million.

Schmidt GA , Girard TD , Kress JP , et al. Official executive summary of an American Thoracic Society/American College of Chest Physicians clinical practice guideline: liberation from mechanical ventilation in critically ill adults. *Am J Respir Crit Care Med*. 2017;195:115–119.

This is a combined Society guideline that provides evidence-based recommendations on elements crucial to the ventilator liberation process. It provides recommendations as answers to questions regarding common dilemmas in ventilator liberation. As a clinical practice guideline, the reader should expect updates as new information becomes available.

Yang KL , Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med*. 1991;324:1445–1450.

Probably the best study of so-called weaning parameters. The authors demonstrated a high sensitivity and moderately high specificity of the respiratory rate to tidal volume ratio (the "rapid shallow breathing index") in predicting successful weaning, defined as the ability to breathe spontaneously for 24 hours following extubation. The overall impact of the study is helped by relatively easy-to-remember cutoff value of 100.

Kuriyama A , Jackson JL , Kamei J. Performance of the cuff-leak test in adults in predicting post-extubation airway complications: a systematic review and meta-analysis. *Crit. Care* 2020;24(1): 640.

An updated meta-analysis looked at the testing characteristics of the cuff-leak test for predicting post-extubation airway obstruction and reintubation. Sensitivity and specificity for predicting upper airway obstruction were 0.62 and 0.87, respectively. Sensitivity and specificity for predicting reintubation were 0.66 and 0.88, respectively. No clear standard for the performance of the cuff-leak test has been established. Therefore, different studies yield markedly different results depending on what technique is used.

Esteban A , Frutos-Vivar F , Ferguson ND , et al. Non-invasive positive pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350:2452–2460.

Two hundred twenty-one patients who developed respiratory failure within 48 hours after planned extubation were randomly assigned to receive either non-invasive ventilation or standard therapy. Rates of reintubation were no different between the groups, but the time to reintubation was longer in the non-invasive ventilation group and the ICU mortality was higher. This study suggests that non-invasive ventilation should not be used as a rescue therapy in patients that develop respiratory failure after extubation.

Ferrer M , Sellares J , Valencia M , et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet* . 2009;374:1082–1088.

One hundred six patients intubated for hypercapnic respiratory failure were randomized to receive either non-invasive ventilation or standard care immediately following planned extubation. Patients randomized to non-invasive ventilation showed lower rates of respiratory failure and 90-day mortality. The important feature was the immediate and uniform, not rescue-based use of the non-invasive ventilation.

Hernandez G , Vaquero C , Colinas L , et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. *JAMA*. 2016;316(15):1565–1574.

Six hundred four patients considered high risk for reintubation were randomized at extubation to receive either non-invasive ventilation of high-flow nasal cannula oxygen. The two groups showed no difference in the rate of reintubation, the median time to reintubation or the incidence of respiratory failure following intubation. The study incorporated a wider range of risk factors for reintubation than other similar studies. Given the relative comfort and convenience of high flow oxygen compared to non-invasive ventilation, this study supports its use in a broad spectrum of post-extubation scenarios.

Girard TD , Kress JP , Fuchs BD , et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371:126–134.

Three hundred thirty-six patients were randomly assigned to receive either a daily interruption of sedation closely followed by a spontaneous breathing trial or to receive sedation practice unrelated to the timing of the spontaneous breathing trial. Subjects in the experimental/paired group had more days breathing independently in the first 28 days after enrollment, had shorter length of ICU and hospital stay and improved mortality out to 1 year after enrollment. This study highlights the impact of sedation as a barrier to weaning and demonstrates an approach to minimize that effect.

Devlin JW , Skrobik Y , Gelinas C , et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46:e825–e873.

This is a multidisciplinary update of the 2013 Pain, Agitation and Delirium Guideline published in 2013. It has added sections related to mobility and sleep as an acknowledgment of the interrelated nature of these with sedation practice in critical care. As a clinical practice guideline, the reader should expect updates as new information becomes available.

Schweikert WD , Pohlman MC , Pohlman AS , et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373:1874–1882.

One hundred four patients were randomized to either daily interruption of sedation plus exercise and mobilization performed by physical and occupational therapists or to daily interruption of sedation without standard mobility therapy. The early mobility group showed a greater return to independent function, lower burden of delirium, and faster weaning from the ventilator. Clinical application of these findings depends on either a substantial investment in physical and occupational therapists or the incorporation of these activities into the daily responsibilities of bedside nurses and nursing assistants.

Pulmonary Embolism

Allen CJ , Murray CR , Meizoso JP , et al. Surveillance and early management of deep vein thrombosis decreases rate of pulmonary embolism in high-risk trauma patients. *J Am Coll Surg*. 2016 Jan;222(1):65–72. doi: 10.1016/j.jamcollsurg.2015.10.014. Epub 2015 Nov 4. PMID: 26616034.

This observational study sought to compare rate of PE after implementation of a weekly venous duplex ultrasound (VDU) protocol versus symptomatic in 402 high-risk trauma patients admitted to the ICU over a 3-year period. All patients underwent screening with

Greenfield's Risk Assessment Profile for VTE risk. Patients with RAP scores greater than or equal to 10 were recommended by the research team to undergo weekly bilateral VDU. There were 259 patients who underwent VDU and 143 did not. DVT rate was 11.6% in the VDU group vs 2.1% in the non-surveillance group. PE rate was 1.9% in the VDU group vs 7% in the non-surveillance group. The group concluded that high-risk trauma patients undergoing weekly VDU were diagnosed and treated for DVT earlier, leading to a lower rate of PE in that group.

Bergqvist D , Agnelli G , Cohen AT , et al. ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med.* 2002 Mar 28;346(13):975–980. doi: 10.1056/NEJMoa012385. PMID: 11919306.

In this double-blind, multicenter, randomized controlled trial, patients undergoing planned curative open surgery for abdominal or pelvic cancer received 6–10 days of open treatment enoxaparin. Then during the double-blind treatment period, patients were randomized to enoxaparin prophylaxis versus placebo for 19–21 days. Results show a decrease in VTE rate (12.0% in placebo group vs 4.8% in enoxaparin group, p = 0.02). This difference was consistent at 3 months postoperatively and there was no difference between groups in adverse events including rate of bleeding events. VTE prophylaxis for 4 weeks post operatively is safe and reduces VTE occurrences.

Bloomer TL , El-Hayek GE , McDaniel MC , et al. Safety of catheter-directed thrombolysis for massive and submassive pulmonary embolism: Results of a multicenter registry and meta-analysis. *Catheter Cardiovasc Interv.* 2017;89(4):754–760.

Bloomer et al. reviews catheter-directed thrombolysis (CDT) data in two forms: patients diagnosed with acute PE and treated with CDT from a multicenter registry and meta-analysis of all contemporary studies utilizing CDT for pulmonary embolism (PE). Efficacy was measured by change in invasive pulmonary artery systolic pressure (PASP) and safety outcomes were listed as any major complication including fatal intracranial hemorrhage (ICH), intraocular or retroperitoneal hemorrhage or any overt hemorrhage that required blood transfusion or surgical repair. The same safety outcomes were evaluated in the registry and the meta-analysis. Results support use of CDT in PE given significant improved in PASP and its low risks. Special care must be taken since patients older than age 75 are at higher risk of ICH. However, more research is needed to compare CDT to anticoagulation alone or systemic thrombolysis.

Decousus H , Leizorovicz A , Parent F , et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med*. 1998 Feb 12;338(7):409–415. doi: 10.1056/NEJM199802123380701. PMID: 9459643.

In this multicenter, randomized trial over 4 years, efficacy and safety of IVC filter placement in prevention of PE was tested in patients with known proximal DVT. Treatment groups included therapeutic unfractionated heparin, therapeutic low-molecular weight heparin (LMWH), IVC filter placement and no filter placement. Primary outcome was occurrence of symptomatic or asymptomatic PE within first 12 days after randomization. This study showed an initial efficacy in filter use for prevention of PE in patients with high-risk proximal DVT receiving anticoagulation. However, no difference in mortality was identified between filter and no filter groups. Lastly, after 2 years, filter patients developed post-phlebitic syndrome and a significant increase in recurrent DVT, possibly related to thrombosis at the filter site.

Es, NV , Coppens M , Schulman S , Middeldorp S , Buller, HR. Direct oral anticoagulants compared with vitamin K antagonist for acute venous thromboembolism: evidence from phase 3 trials. *Blood* . 2014;124(12):1968–1975.

This meta-analysis reviews six phase 3 trials comparing direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) in treatment of acute VTE. Over 13,500 patients were randomized to both the DOAC and VKA arms for a total of 27,023 patients. There was no difference in VTE recurrence between DOACs and VKAs. Major bleeding events including intracranial hemorrhage and gastrointestinal hemorrhage were decreased in the DOAC therapy arm. DOAC efficiency was consistent across multiple patient subgroups including weight >100 kg, cancer, moderately impaired renal clearance (CrCl 30-49 mL/min) and patients age >75. DOACs are clearly noninferior to VKA therapy for treatment of acute VTE.

Ginzburg E , Cohn SM , Lopez J , Jackowski J , Brown M , Hameed SM ; Miami Deep Vein Thrombosis Study Group. Randomized clinical trial of intermittent pneumatic compression

and low molecular weight heparin in trauma. *Br J Surg*. 2003 Nov;90(11):1338–1344. doi: 10.1002/bjs.4309. PMID: 14598411.

This prospective randomized trial compared intermittent pneumatic compression (IPC) devices and low-molecular weight heparin (LMWH) in trauma patients at high risk for VTE. Patients underwent admission screening DVT ultrasound of the bilateral lower extremities (popliteal, saphenous, femoral, and iliac veins) and then weekly thereafter. Patients were followed until hospital discharge or 30 days from admission or death, whichever occurred first. Rate of PE was similar in both groups and not statistically significant. The study showed comparable effects of both methods of thromboprophylaxis.

Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012 May 12;379(9828):1835–46. doi: 10.1016/S0140-6736(11)61904-1. Epub 2012 Apr 10. PMID: 22494827.

In this review paper, Dr. Goldhaber covers the extensive topic of pulmonary embolism from epidemiology to treatment with thrombolysis and thrombectomy. His expertise on the topic is evident and this comprehensive article is an up-to-date resource and tool for physicians everywhere.

Kashuk JL , Moore EE , Sabel A , et al. Rapid thromboelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. *Surgery* . 2009;146(4):764 – 774.

In this retrospective analysis over 7 months, 152 surgical patients in the intensive care unit were assessed as hypercoagulable or not by rapid thromboelastography (r-TEG). 67% (86 patients) were found to be hypercoagulable by r-TEG. Hypercoagulable patients had risk factors including high-risk injury, spinal cord injury, longer median ICU stay, longer median ventilatory days, and longer hospital length of stay. Nineteen percent (16 patients) in the hypercoagulable group suffered thromboembolic events and 12% (10 patients) had thromboembolic events predicted by prior r-TEG. Patients with normal coagulability did not suffer any thromboembolic events.

Meyer G , Vicaut E , Danays T , et al. Fibrinolysis for patients with intermediate risk pulmonary embolism. *N Engl J Med.* 2014;370(15):1402–1411.

The multicenter, randomized, double-blind trial compared efficacy and safety between fibrinolysis with a bolus of systemic Tenecteplase plus anticoagulation versus anticoagulation with placebo in patients with intermediate-risk pulmonary embolism. Primary efficacy outcomes were all-cause mortality and hemodynamic decompensation. Primary safety outcomes were major bleeding events or stroke (ischemic or hemorrhagic). Results showed a single dose of Tenecteplase did reduce risk of early death or hemodynamic decompensation. However, Tenecteplase use is associated with a significant increase in intracranial hemorrhage and other major bleeding. Patients >75 did have higher risk of bleeding. Decreasing the Tenecteplase dose by half may reduce this risk, but further research is needed. Fibrinolysis is effective but comes at a cost.

Mismetti P , Laporte S , Pellerin O , et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA* . 2015;313(16):1627–1635.

This randomized trial compared treatment with inferior vena cava (IVC) filters plus anticoagulation versus anticoagulation alone on risk of recurrent pulmonary embolism. Primary outcome was death or recurrent symptomatic PE at 3 months. At that time point, in the IVC filter group, 3% (6 patients) developed recurrent PE and all cases were fatal. In the anticoagulation only group, 1.5% (3 patients) developed recurrences and 2 out of the 3 were fatal. There were no statistical differences between the groups and IVC filter placement in addition to anticoagulation did not reduce risk of recurrent pulmonary embolism.

Obi AT , Pannucci CJ , Nackashi A , et al. Validation of the Caprini venous thromboembolism risk assessment model in critically ill surgical patients. *JAMA Surg.* 2015;150(10):941–948.

This 5-year retrospective review of over 4800 critically ill patients at a tertiary academic hospital evaluated the validity of the Caprini score on venous thromboembolism (VTE) risk assessment at time of ICU admission. This is based on the 2005 Caprini RAM score. Results show increased incidence of VTE linearly with increasing Caprini score. The Caprini score is a valid and reliable tool in critically ill surgical patients.

Yoo HH , Nunes-Nogueira VS , Fortes Villas Boas PJ. Anticoagulant treatment for subsegmental pulmonary embolism. *Cochrane Database Syst Rev*. 2020 Feb

7;2(2):CD010222. doi: 10.1002/14651858.CD010222.pub4. PMID: 32030721; PMCID: PMC7004894.
This is a 2020 Cochrane review of multiple databases for randomized controlled trials assessing anticoagulation treatment versus placebo in patients with subsegmental pulmonary embolism (SSPE). However, no RCTs were identified in this area. Therefore, there is no evidence from randomized controlled trials to assess the efficacy or safety of either anticoagulation or active surveillance/observation. Clinical equipoise must be used in each patient encounter given the patient's clinical status in addition to risks and benefits of each treatment plan.

Extracorporeal Membrane Oxygenation

Combes A , Peek GJ , Hajage D , et al. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. *Intensive Care Med.* 2020 Oct 6;0–11.
Systematic review and individual patient data meta-analysis of two RCTs (CESAR and EOLIA) combining data from 429 patients. Showing that 90-day mortality was significantly lowered by ECMO compared with conventional management.
Ferguson ND , Fan E , Camporota L , et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med.* 2012 Oct 1;38(10):82–1573.
Most current consensus on the definition of ARDS.
Bellani G , Laffey JG , Pham T , et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA.* 2016 Feb 23;315(8):788.
International, multicenter, prospective cohort study of patients undergoing invasive or noninvasive ventilation, conducted in 459 ICUs from 50 countries across 5 continents. Included 29,144 patients admitted to participating ICUs. The period prevalence of ARDS was 10.4% of ICU admissions. This syndrome appeared to be underrecognized and undertreated and associated with a high mortality rate.
Herridge MS , Tansey CM , Matté A , et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 2011 Apr 7;364(14):304–1293.
Prospective, longitudinal cohort study of that evaluated 109 survivors of ARDS at 3, 6, and 12 months and at 2, 3, 4, and 5 years after discharge from the intensive care unit. Showing that physical and psychological problems developed or persisted in patients and family caregivers for up to 5 years.
Gattinoni L , Tonetti T , Cressoni M , et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med.* 2016 Oct 1;42(10):75–1567.
The mechanical power equation encompasses the different ventilator-related causes of lung injury and of their variations and can be easily adapted to most ventilators.
Abrams D , Schmidt M , et al. Mechanical ventilation for acute respiratory distress syndrome during extracorporeal life support. Research and practice. *Am J Respir Crit Care Med.* 2020 Mar 1;201(5):25–514.
Narrative review reflecting the consensus of expert opinions of clinicians and researchers with expertise in mechanical ventilation, ARDS, and ECLS that originated from a roundtable discussion at the 4th Annual International ECMO Network Scientific Meeting in Rome, Italy in 2018, regarding mechanical ventilation for ARDS patients undergoing ECMO support.
Peek GJ , Mugford M , Tiruvoipati R , et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* . 2009 Oct 17;374(9698):63–1351.
The CESAR study was the first of the modern RCTS supporting ECMO as a valid treatment option for the management of patients with severe respiratory failure. However, it does not show that ECMO is better than conventional ventilation. It does show benefit of transferring these patients to specialized ECMO centers.

Goligher EC , Tomlinson G , Hajage D , et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *JAMA* . 2018 Dec 4;320(21):2251.
Bayesian inference directly estimates the probability that a conclusion is true given the data observed in an experiment. Bayesian analyses support a consensus that ECMO lowers mortality but, at the same time, demonstrate that there remains substantial variability in the conclusions to be drawn regarding whether ECMO confers a large benefit.
Wilcox ME , Jaramillo-Rocha V , Hodgson C , Taglione MS , Ferguson ND , Fan E . Long-term quality of life after extracorporeal membrane oxygenation in ARDS survivors: systematic review and meta-analysis. *J Intensive Care Med.* 2020 Mar;35(3):43–233.
Systematic Review and Meta-Analysis showing greater decrements in health-related quality of life were seen for survivors of ECMO when compared to survivors of conventional mechanical ventilation, on the contrary those who received ECMO experienced significantly less psychological morbidity.
Schmidt M , Hajage D , Lebreton G , et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med*. 2020;8(11):1121–31.
Retrospective cohort study performed in five French ICUs and included patients who received ECMO for COVID-19 associated ARDS. Showing that the estimated 60-day survival of ECMO-rescued patients with COVID-19 was similar to that of previous studies for patients with severe ARDS suggesting that ECMO can be considered for refractory respiratory failure in this cohort of patients.

Perioperative Arrhythmias

Koshy AN, Hamilton G , Theuerle J , et al. Postoperative atrial fibrillation following noncardiac surgery increases risk of stroke. *Am J Med.* 2020;133:22–311.
This 14 study meta-analysis of over 3 million patients demonstrated that postoperative atrial fibrillation correlates with stroke risk and this association was stronger with noncardiac nonthoracic surgery compared with thoracic surgery.
Echahidi N , Pibarot P , O'Hara G , Mathieu P . Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol*. 2008;51:793–801.
This comprehensive review article discusses the morbidity associated with postcardiac surgery atrial fibrillation along with various prevention and treatment modalities.
Villareal RP , Hariharan R , Liu BC , et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol*. 2004;43:2–874.
The single-center retrospective review article of over 6000 post-CABG patients demonstrated a significantly higher mortality among the 16% of patients who developed atrial fibrillation.
Siontis KCG , Gersh BJ, Weston , SA, et al. Association of new-onset atrial fibrillation after noncardiac surgery with subsequent stroke and transient ischemic attack. *JAMA* . 2020;324:1–887.
This retrospective cohort study of 904 patients post noncardiac surgery demonstrated a statistically significant hazard ratio (2.69) for stroke among patients who developed postoperative atrial fibrillation versus those who did not.
El-Chami MF , Kilgo P , Thourani V , et al. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. *J Am Coll Cardiol*. 2010;55:6–1370.
This seminal large retrospective study of over 16,000 patients demonstrated that, despite controlling for 32 variables, warfarin use was associated with a lower mortality for new onset atrial fibrillation after CABG compared to no anticoagulation use.
Butt JH , Xian Y , Peterson ED , et al. Long-term thromboembolic risk in patients with postoperative atrial fibrillation after coronary artery bypass graft surgery and patients with nonvalvular atrial fibrillation. *JAMA Cardiol*. 2018;3:24–417.
Utilizing a comprehensive Danish nationwide database, this study demonstrated that compared to age, sex, and CHA2DS2-VASc score matched patients in the database with non-valvular non-surgical AF, those with post-CABG atrial fibrillation had lower rates of

thromboembolism (Adjusted HR 0.55, 95%CI 0.32–0.95).

Butt JH , Olesen JB , Gundlund A , et al. Long-term thromboembolic risk in patients with postoperative atrial fibrillation after left-sided heart valve surgery. *JAMA Cardiol*. 2019;4:47–1139.

Utilizing a comprehensive Danish nationwide database, this study demonstrated that compared to age, sex, and CHA2DS2-VASc score matched patients in the database with non-valvular non-surgical AF, those with post-valvular surgery atrial fibrillation had similar rates of thromboembolism (HR 1.22, 95%CI 0.88–1.68).

Butt JH , Olesen JB , Havers-Borgersen E , et al. Risk of thromboembolism associated with atrial fibrillation following noncardiac surgery. *J Am Coll Cardiol*. 2018;72:36–2027.

Utilizing a comprehensive Danish nationwide database, this study demonstrated that compared to age, sex, and CHA2DS2-VASc score matched patients in the database with non-valvular non-surgical AF, those with post-noncardiac surgery atrial fibrillation had similar rates of thromboembolism (HR 0.95, 95%CI 0.85–1.07).

Matos JD , McIlvaine S , Grau-Sepulveda M , et al. Anticoagulation and amiodarone for new atrial fibrillation after coronary artery bypass grafting: prescription patterns and 30-day outcomes in the United States and Canada. *J Thorac Cardiovasc Surg*. 2020.

Utilizing the Society for Thoracic Surgeons database, this large retrospective study demonstrated that a majority of clinicians treat patients with amiodarone and no anticoagulation for new post-CABG atrial fibrillation at discharge. Within the first 30 days, the bleeding risk associated with anticoagulation appears to far outweigh the potential for stroke reduction.

Congestive Heart Failure

Berg DD , Bohula EA , van Diepen S , et al. Epidemiology of shock in contemporary cardiac intensive care units. *Circ: Cardiovasc Qual Outcomes*. 2019 March;12(3):e005618. doi:10.1161/CIRCOUTCOMES.119.005618

This was a cross-sectional study from 16 centers in the Critical Care Cardiology Trials Network with >3000 patients admitted to cardiac intensive care units where 2/3 of patients had evidence of cardiogenic shock and nearly half of those were patients with decompensated HFrEF.

Nohria A , Tsang SW , Fang JC , et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol*. 2003;41(10):1797–1804.

This was a single-center, prospective cohort study of 452 patients admitted to Brigham and Women's Hospital with HFrEF where hemodynamic categorization based on congestion and systemic perfusion using bedside clinical assessment identified distinct profiles of risk. Patients with congestion and decreased perfusion (i.e., “cold and wet”) had the highest mortality over the subsequent 18 months.

Garan AR , Kanwar M , Thayer KL , et al. Complete hemodynamic profiling with pulmonary artery catheters in cardiogenic shock is associated with lower in-hospital mortality. *Heart Failure*. 2020;8(11):903–913.

This was a retrospective cohort study of >1400 patients admitted with cardiogenic shock from the Cardiogenic Shock Working Group, a multicenter collaboration of academic medical centers. Patients with cardiogenic shock who were managed with a pulmonary artery catheter with complete hemodynamic profiling had a significantly lower inpatient mortality.

Mullens W , Abrahams Z , Francis GS , et al. Sodium nitroprusside for advanced low-output heart failure. *J Am Coll Cardiol*. 2008;52(3):200–207.

This was a retrospective, case-control study of patients admitted with decompensated HFrEF and low cardiac output at Cleveland Clinic. Compared to control patients who were managed with traditional medical therapy, patients who received sodium nitroprusside had significantly greater hemodynamic improvement, were more likely to be discharged on an oral vasodilator, and had improved long-term survival.

McMurray JJ , Packer M , Desai AS , et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* Sep 2014;371(11):993–1004. doi:10.1056/NEJMoa1409077

PARADIGM-HF was a landmark, randomized clinical trial of ARNI therapy with sacubitril-valsartan compared to traditional ACE inhibitor (enalapril) in 8442 HFrEF patients with NYHA class ≥2 symptoms, LVEF <40%, elevated BNP, and receiving stable doses of a beta-blocker and ACE inhibitor or ARB (equivalent in dose to enalapril 10 mg daily). The trial was stopped early, after a median follow-up at 27 months, due to overwhelming benefit with ARNI therapy, including a lower incidence of the primary outcome of cardiovascular death or HF hospitalization (21.8% vs. 26.5%; p <0.001, number needed to treat of 21), a significant reduction in all-cause mortality (17.0% vs. 19.8%; p <0.001, number needed to treat of 36), and better quality of life scores.

Velazquez EJ , Morrow DA , DeVore AD , et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 02 2019;380(6):539–548. doi:10.1056/NEJMoa1812851

PIONEEF-HF was a randomized clinical trial of 881 patients admitted with decompensated HFrEF who were hemodynamically stable, defined as not requiring increasing doses of IV diuretics, vasodilators, or inotropes within 24 hours prior to randomization. Compared to patients in the control arm treated with enalapril, patients receiving ARNI therapy (sacubitril-valsartan) had significantly greater reductions in NTproBNP after 8 weeks of therapy (percent change −25.3% with enalapril versus −46.7% with sacubitril-valsartan, ratio of change 0.71, 95%CI 0.63–0.81, p <0.001).

Morrow DA , Velazquez EJ , DeVore AD , et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF Trial. *Circulation* . 2019 May;139(19):2285–2288. doi:10.1161/CIRCULATIONAHA.118.039331

This secondary analysis of the PIONEEF-HF trial demonstrated that patients randomized to sacubitril-valsartan (ARNI) compared to enalapril (ACEi) had a significantly lower rate of the combined endpoint of death, re-hospitalization for HF, left ventricular assist device implantation, or listing for cardiac transplant (hazard ratio 0.58, 95% CI 0.40–0.85, p = 0.005).

Mann DL , Greene SJ , Givertz MM , et al. Sacubitril/valsartan in advanced heart failure with reduced ejection fraction: rationale and design of the LIFE trial. *JACC Heart Failure*. 10 2020;8(10):789–799. doi:10.1016/j.jchf.2020.05.005

The ongoing LIFE Trial is a 24-week, prospective, multicenter, double-blinded, double-dummy, active comparator trial of sacubitril-valsartan versus valsartan alone in patients with severe HFrEF defined as LVEF ≤35%, NYHA class IV symptoms, and at least one or more objective findings of "advanced" heart failure: 1) current inotropic support or need for inotropes within the past 6 months, 2) at least one hospitalization for heart failure in the last 6 months, 3) LVEF ≤25%, 4) peak VO2 <55% predicted or ≤16 mL/kg/min for men or ≤14 mL/kg/min for women, 5) 6-minute walk distance <300 m.

Gu J , Noe A , Chandra P , et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol*. Apr 2010;50(4):401–414. doi:10.1177/0091270009343932

This is a review of the basic pharmacokinetics and pharmacodynamics of sacubitril-valsartan.

Haynes R , Judge PK , Staplin N , et al. Effects of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease. *Circulation* . 10 2018;138(15):1505–1514. doi:10.1161/CIRCULATIONAHA.118.034818

The UK HARP-III study was a randomized, double-blind trial of 414 patients with chronic kidney disease and estimated glomerular filtration rate (eGFR) of 20–60 mL/min/1.73m2 who were randomized to traditional ARB with irbesartan versus ARNI with sacubitril-valsartan. The primary outcome of eGFR at 12 months as well as urine albumin:creatinine was similar in both groups, and ARNI therapy was associated with significantly lower follow-up levels of troponin-I and NTproBNP.

Perioperative Myocardial Infarction

Collett JP , Thiele H , Barbato E , et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2021;42(14):1289–1367.

This is the most recent societal guideline summarizing evidence and recommendations for the various aspects of management of myocardial infarction with ST-segment elevation. This comprehensive document can serve as a reference for the practicing intensivist.

Ferreira, T , Arede, MJ , Oliveira, F , et al. Myocardial infarction after noncardiac surgery, a 10 year experience. Eur J Anaesthesiol. 2013;30:72.

This analysis provides special context for differences in the presentation of perioperative vs. spontaneous myocardial infarction as well as the frequency and associated mortality.

Freemantle N , Cleland J, Young P, Mason J, Harrison J. Beta Blockade after myocardial infarction: systematic review and meta regression analysis. Br Med J. 1999;318(7200):17.

This review summarizes over 20 years of randomized trials evaluating the benefits and risks of beta-blockade after myocardial infarction. A 23% reduction in the odds of death in long term trials (95% confidence interval 15% to 31%), and a 4% reduction in the odds of death in short term trials ([-]8% to 15%). In long term trials, the number needed to treat for 2 years to avoid a death is 42.

Hofmann R , James, SK , Jernberg, T , et al. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med. 2017;377(13):1240–1249.

The Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction (DETO2X-AMI) was a multicenter, randomized control trial with a total of 6629 patients assigned to either oxygen or ambient-air group. All-cause mortality at 1 year was similar in the oxygen and ambient air groups (5.0% vs. 5.1%; HR 0.97; p = 0.80), as was MI rehospitalization at 1 year (3.8% vs. 3.3%; HR p = 0.33). The trial suggests avoiding routine use of oxygen among patients with normoxia and MI or findings concerning for MI.

Mehta SR , Granger CB , Boden WE , et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med. 2009;360(21):2165–2175.

A number of randomized trials demonstrated the benefit of early invasive intervention with angiography in high-risk patients with unstable angina (UA) and NSTEMI. This trial evaluated timing of this intervention. The trial randomized 3031 patients with unstable angina or NSTEMI to either early-intervention (as early as possible and <24 hours) or delayed-intervention (minimum delay of 36 hours). At 6 months, the primary outcome (composite of death, new MI, or stroke) occurred in 9.6% of patients in the early-intervention group compared to 11.3% in the delayed-intervention group (HR 0.95; 95% CI 0.68 to 1.06; p = 0.15). A prespecified subgroup analysis showed the highest risk patients undergoing early intervention had a significantly lower rate of the primary outcome compared to those in the delayed intervention arm (13.9% vs. 21.0% HR 0.65, CI 0.48 to 0.89, p = 0.006). When this same subgroup analysis was applied to low- to moderate-risk patients, there was no significant difference in the primary outcome between early or delayed intervention. This trial informs perioperative management decisions with regard to timing in the perioperative setting where the magnitude of benefit according to risk can be balanced against the harms associated with performing angiography and administering anticoagulants.

Thygesen K , Alpert JS , Jaffe AS , et al . Fourth universal definition of myocardial infarction. J Am Coll Cardiol. 2018;72(18):2231–2264.

This consensus document outlines the definitions and pathophysiologic differences in the various forms of myocardial infarction. Of particular interest to intensivists are the distinctions between spontaneous, Type I infarctions, and Type II infarctions secondary to supply/demand mismatch. Infarctions related to stent thrombosis, sudden death, and after coronary artery bypass surgery are also discussed.

Blood Pressure Control in Acute Stroke

Filho JO , Mullen MT . Initial assessment and management of acute stroke. http://www.uptodate.com. Accessed 12/26/2020

Overview of the management of both ischemic and hemorrhagic stroke.

Nasi LA , Martins SCO , Gus M , et al. Early manipulation of arterial blood pressure in acute ischemic stroke (MAPAS): results of a randomized controlled trial. Neurocrit Care. 2019;30:70–372. PMID: 30460598

A relatively small prospective evaluating the effect of three different targets for blood pressure control. Good clinical outcome was not different among the three groups. However, symptomatic intracranial hemorrhage was more common in the higher blood pressure group. Adjusted logistic regression suggested the odds of having a good clinical outcome was higher in the group where a blood pressure range of 161–180 mm Hg was attained.

Bath PM , Scutt P , Anderson CS , et al. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomized, sham-controlled, blinded, phase 3 trial. Lancet. 2019;393(10175):20–1009. PMID: 30738649

Prehospital administration of transdermal nitroglycerin did not improve the modified Rankin scores in stroke patients compared to placebo. In addition, there was no difference in secondary outcomes and death. Almost half did not have an ischemic stroke and included hemorrhagic stroke, transient ischemic attack and non-stroke mimic.

Powers WJ , Rabinstein AA , Ackerson T , et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guidelines for healthcare professionals from the American Heart Associate/American Stroke Association. Stroke. 2019;50:3344–e418. PMID: 31662037

Consensus guidelines for the early management of acute ischemic stroke.

Schonenberger S , Uhlmann L , Hacke W , et al. Effect of conscious sedation versus general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy: a randomized clinical trial. JAMA. 2016;316:96–1986. PMID: 27785516

Prospective, single-center, randomized, parallel-group, open-label treatment trial comparing the effect of GA versus MAC on outcome following endovascular thrombectomy in patients with anterior circulation ischemic strokes. A total of 150 patients were randomized. There was no difference in the 24 hour National Institutes of Health Stroke Scale (NIHSS) score between the groups. Most secondary outcomes were not different either. However, patient movement was less in the GA group whereas hypothermia, delayed extubation, and pneumonia were more common. At 3 months, more GA patients were functionally independent based on the modified Rankin Scale but there was no difference in mortality.

Henden PL , Rentzos A , Karlsson J-E , et al. General anesthesia versus conscious sedation for endovascular treatment of acute ischemic stroke. The AnStroke Trial (anesthesia during stroke). Stroke. 2017;48:07–1601. PMID 28522637

Prospective, randomized, single-center study comparing general anesthesia (GA) to conscious sedation during endovascular treatment of ischemic stroke. There were 45 patients in each group. There was no difference in the modified Rankin Scale score at 3 months. Mean arterial blood pressure was significant lower in the GA group and use of vasopressor support was more common.

Anderson CS , Heeley E , Huang Y , et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368:65–2355. PMID: 23713578

Large multicenter, randomized trial comparing two systolic BP goals (<140 [intensive treatment] versus <180 mm Hg) within one hour in patients suffering from a hemorrhagic stroke. At 90 days, those in the intensive treatment group had a lower modified Rankin Scale as determined by ordinal analysis but there was no difference in mortality between the groups.

Qureshi AI , Palesch YY , Barsan WG , et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375:43–1033. PMID 27276234
Prospective, randomized trial comparing intensive systolic BP control (SBP, 110–139 mm Hg) to standard SBP control (140–179 mm Hg) within 4.5 hours of symptom onset in patients with intracerebral hemorrhage. At 3 months, there was no difference in the modified Rankin Scale or mortality between the groups. Serious adverse events within the first 72 hours after randomization were no different although adverse renal events were noted in the intensive treatment group in the first 7 days.
Hemphill JC III , Greenberg SM , Anderson CS , et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association and American Stroke Association. Stroke. 2015;46:60–2032. PMID: 26022637
Consensus guidelines which include guidance for blood pressure control in patients with spontaneous intracerebral hemorrhage.

Mechanical Circulatory Support

Helman DN , Rose EA . History of mechanical circulatory support. Prog Cardiovasc Dis. 2000;43(1):1–4.
This review article provides a detailed history of the early development of mechanical support devices through the late 1990s.
Combes A , Price S , Slutsky AS , Brodie D . Temporary circulatory support for cardiogenic shock. Lancet. 2020;396(10245):199–212.
A comprehensive review article focused on temporary mechanical circulatory support devices
.
Rose EA , Gelijns AC , Moskowitz AJ , et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–1443.
A multicenter, randomized, controlled trial of patients with end-stage heart failure ineligible for transplantation, comparing treatment with LVAD (n = 68) to optimal medical therapy (n = 61). Treatment with a first generation LVAD (HeartMate XVE) reduced all-cause mortality as compared to treatment with optimal medical therapy alone. Mortality was reduced at one year (52% vs. 25%, p = 0.002), but not at 2 years (25% vs. 8%, p = 0.09). Infection and device failure drove mortality in the device group. Patients treated with an LVAD were more likely to have an adverse event than those receiving medical therapy. The device group demonstrated improved quality of life. This study established the benefit of LVADs for destination therapy, leading to FDA approval for this indication in 2002.
Slaughter MS , Rogers JG , Milano CA , et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361(23):2241–2251.
A multicenter, randomized, controlled trial of patients with advanced heart failure ineligible for transplantation treated with either a second-generation axial continuous-flow device (HeartMate II, n = 134) or the device approved at the time, a first generation pulsatile-flow device (HeartMate XVE, n = 66). In the continuous-flow group, 46% of patients reached the primary composite endpoint of survival free from disabling stroke or need for reoperation for device replacement or repair, as compared to 11% in in the pulsatile-flow group (p <0.001). Failure to reach the primary outcome was driven by need for reoperation and death. Adverse events including infection, right heart failure, and rehospitalization were reduced in the continuous-flow group. There was no reduction in stroke or bleeding. Both groups demonstrated improvement in quality of life metrics.
Starling RC , Moazami N , Silvestry SC , et al. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med. 2014;370(1):33–40.
A retrospective study examining data from 837 HeartMate II patients at three institutions. This study demonstrated an increased rate of pump thrombosis associated with substantial mortality if not treated with device replacement or transplantation. A marked increase in lactate dehydrogenase levels often preceded new pump thrombosis.

Rogers JG , Pagani FD , Tatooles AJ , et al. Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med. 2017;376(5):451–460.
A multicenter, randomized, controlled trial of patients with advanced heart failure ineligible for transplantation comparing a centrifugal continuous-flow LVAD with hydrodynamic and magnetic levitation (HeartWare HVAD, n = 297) to the commercially available axial continuous-flow LVAD (HeartMate II, n = 148). The study showed non-inferiority of the centrifugal-flow device relative to the axial-flow device with respect to the primary composite endpoint of two-year survival free from disabling stroke or need for reoperation due to pump malfunction or failure. Strokes of any severity and RV failure were more frequent in patients in the centrifugal-flow group; patients receiving the axial-flow device more frequently required reoperation. Both groups had improved quality of life metrics. Post-hoc analysis of the centrifugal-flow group demonstrated patients with mean arterial pressure <90 mmHg had lower incidence of stroke.
Teuteberg JJ , Cleveland JC, Jr. , Cowger J , et al. The society of thoracic surgeons Intermacs 2019 annual report: the changing landscape of devices and indications. Ann Thorac Surg. 2020;109(3):649–660.
The Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs) is a North American registry that prospectively collects data on all patients who received a Food and Drug Administration-approved mechanical circulatory support device. This annual report provides longitudinal granular data including clinical characteristics and outcomes according to device type. This is the most recent annual report at the time of this writing, and examines data from the period of January 2014 through September 2019, reflecting contemporary experience.
Stevenson LW , Pagani FD , Young JB , et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant. 2009;28(6):535–541.
A classification system according to illness severity for advanced heart failure patients being considered for mechanical circulatory support.
Goldstein DJ , Meyns B , Xie R , et al. Third annual report from the ISHLT Mechanically Assisted Circulatory Support Registry: a comparison of centrifugal and axial continuous-flow left ventricular assist devices. J Heart Lung Transplant. 2019;38(4):352–363.
The International Society for Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) Registry collects global data on patients receiving durable mechanical support devices. Intermacs (reference 7) contributes data to this registry, as do registries from Europe, Japan, and the UK. Twenty-four additional hospitals also provide data to the registry. The report includes longitudinal granular data including clinical characteristics and outcomes according to device types. The report includes data from the time of the registry inception in 2013 through the end of 2017.

Severe Electrolyte Disturbances

Verbalis JG , Goldsmith SR, Greenbrg A , et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1–42.
https://pubmed.ncbi.nlm.nih.gov/24074529/
United States expert guidelines on hyponatremia include a recommendation to increase the serum sodium only 4–6 mmol/L/24 h for severe hyponatremia.
Baek SH , Jo YH , Medina-Liabres K , Oh YK , Lee JB , Kim S . Risk of overcorrection in rapid intermittent bolus vs. slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: the SALSA randomized clinical trial. JAMA Intern Med. 2021 Jan 1;181(1):81–92.
Rafat C , Schortgen F , Gaudry S , Miguel-Montanes R , Bertrand F , Dreyfuss D . Use of desmopressin acetate in severe hyponatremia in the intensive care unit. Clin J Am Soc Nephrol. 2014;9(2):229–237.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3913226/
A retrospective review of 20 patients who received desmopressin as part of their treatment for severe hyponatremia found that desmopressin is effective in slowing the rise of plasma

sodium concentration in severe hyponatremia from a mean of 0.8 mmol/L to 0.02 mmol/L.
MacMillan TE, Cavalcanti RB . Outcomes in severe hyponatremia with and without desmopressin. Am J Med. 2018;131(3):317.e1–317.e10.
https://pubmed.ncbi.nlm.nih.gov/29061503/
A retrospective review of 254 admissions for severe hyponatremia in which desmopressin was used to help slow the rise in serum sodium in a reactive or proactive strategy or for rescue if the serum sodium corrected too quickly.
Palevsky PM , Bhagrath R , Greenberg A . Hypernatremia in hospitalized patients. Annals Int Med. 1996;124:197–203.
A prospective series of just over 100 patients with a serum sodium of 150 or greater, admitted over a 3-month period at a single urban university hospital. Eighteen patients presented with hypernatremia, whereas the rest had hospital-acquired hypernatremia. Those with hypernatremia on presentation were older (mean age 76 vs. 59), more likely to be from a nursing home (61% vs. 9%) and had more severe hypernatremia than those who developed hypernatremia in the ICU.
Linder G, et al. Hypernatremia in the critically ill is an independent risk factor for mortality. Am J Kidney Dis. 2007;50(6):952–7.
https://pubmed.ncbi.nlm.nih.gov/18037096/
In a retrospective series of nearly 1000 ICU patients, 9% had hypernatremia (2% on admission and 7% developed hypernatremia during their ICU stay). The mortality for these patients was significantly higher (39% and 43%, respectively) compared to ICU patients without hypernatremia (24%).
Alshayeb HM, et al. Severe hypernatremia correction rate and mortality in hospitalized patients. Am J Med Sci. 2011;341(5):356–60.
https://pubmed.ncbi.nlm.nih.gov/21358313/
This retrospective review of 131 patients with hypernatremia (>155 mEq/L) found that 90% of patients had a correction rate of <0.5 mEq/L/h but less than 1/3 achieved a serum sodium of <145 after 72 hours of treatment. The overall mortality rate was 37% and multivariate analysis found that slower correction of the serum sodium was an independent predictor of 30-day mortality.
Sterns RH . Evidence for managing hypernatremia: is it just hyponatremia in reverse? Clin J Am Soc Nephrol. 2019; 14(5):5–764.
https://pubmed.ncbi.nlm.nih.gov/31064771/
A well-known expert in the “dysnatremias” explores the evidence for the management of hypernatremia with this cogent editorial of the landmark paper. Dr. Sterns contrasts hypernatremia with hyponatremia and refutes the “quest for symmetry*” that many consider in the care of patients with hypernatremia.*
Kahn A , Brachet E , Blum D . Controlled fall in natremia and risk of seizures in hypertonic dehydration. Intensive Care Med. 1979;5:27–31.
https://pubmed.ncbi.nlm.nih.gov/35558/
A retrospective series of 47 infants who were admitted for dehydration and were treated with intravenous fluids. Nine of these infants experienced seizures (all with a rate of correction >0.7 mEq/h) This report has been heralded as proof that the rate of correction should be <0.5 mmol/h.
Adrogue HJ , Madias NE . Hypernatremia. N Engl J Med. 2000;342:99–1493.
https://www.nejm.org/doi/10.1056/NEJM200005183422006
A popular review of hypernatremia that also outlines the use of an equation which predicts the serum sodium after a liter of IV fluid.

Acute Kidney Injury

Makris K , Spanou L . Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev. 2016;37(2):85–98.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5198510/
This straight-forward review article focuses on the complicated history of defining AKI, multifactorial etiologies of AKI, and our evolving understanding of the pathophysiology.
Awad S , Allison SP , Lobo DN . The history of 0.9% saline. Clin Nutr. 2008;27(2):179–188.
https://www-sciencedirect-com.ezp-prod1.hul.harvard.edu/science/article/pii/S0261561408000289
The authors provide a detailed and exhaustive review of the origins and development of 0.9% saline, including the historical fictions that have been propagated over time and the most important figures in the development of derivative intravenous fluids.
Myburgh JA , Mythen MG . Resuscitation fluids. N Engl J Med. 2013;369:1243–1251.
https://www.nejm.org/doi/full/10.1056/nejmra1208627
The authors provided a detail review of the available resuscitative fluids in the current armamentarium, comparing the evidence for their use. This review article covers a brief history of intravenous fluids, physiology of fluid resuscitation, and a comparison of the intravenous fluids available for the acutely ill patient.
Yunos NM , Bellomo R , Hegarty C , Story D , Ho L , Bailey M . Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566–1572.
https://pubmed.ncbi.nlm.nih.gov/23073953/
This observational pilot study evaluated the use of chloride-liberal solutions (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) versus chloride-restrictive solutions (Hartmann solution, Plasma-Lyte 148, or chloride-poor 20% albumin). Analysis of 1533 ICU patients concluded that a chloride-restrictive fluid strategy was associated with a decrease in the incidence of AKI and the use of renal replacement therapies.
Young P , Bailey M , Beasley R , et al. for the SPLIT Investigators and the ANZICS CTG . Effect of a buffered crystalloid solution vs. saline on acute kidney injury among patients in the intensive care unit. The SPLIT randomized clinical trial. JAMA. 2015;314(16):1701–1710.
https://jamanetwork.com/journals/jama/fullarticle/2454911?guestAccessKey=899f99d9-b1ce-4e49-80b4-85da816d8dfe
This double-blind, cluster randomized, double-crossover trial of saline versus buffered crystalloid solutions evaluated renal complications of ICU patients in four different units in New Zealand. Analysis of 2278 patients did not show any benefit of the use of buffered crystalloid solutions in reducing the incidence of AKI.
Semler MW , Self WH , Wanderer JP , et al.; the SMART Investigators and the Pragmatic Critical Care Research Group . Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378:829–839.
https://www.nejm.org/doi/pdf/10.1056/NEJMoa1711584
The SMART trial randomized 15,802 critically ill adults to receive either 0.9% saline or balanced crystalloids. The use of balanced crystalloids showed slightly more favorable results in a composite outcome of all-cause mortality, new renal replacement therapy, and persistent kidney dysfunction, though the individual outcomes did not reach statistical significance.
Self WH , Semler MW , Wanderer JP , et al. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med. 2018;378(9):819–828. doi:10.1056/NEJMoa1711586
https://www.nejm.org/doi/10.1056/NEJMoa1711586?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
The SALT-ED trial was run by the same investigators of, and in parallel with, the SMART trial. In a total of 13,347 non-critically ill patients, the number of hospital-free days was similar among those who received 0.9% saline versus balanced crystalloids, but there was a lower incidence of major adverse kidney events with balanced crystalloids (over 30 days of follow-up).
Antequera Martín AM , Barea Mendoza JA , Muriel A , et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. Cochrane Database Syst Rev. 2019;7(7):CD012247. Published 2019 Jul 19. doi:10.1002/14651858.CD012247.pub2

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012247.pub2/full
Using strict inclusion criteria, this Cochrane Review meta-analyzed 21 randomized controlled trials of providing 0.9% saline or balanced crystalloids in adults and children in the critical care setting. The authors concluded that there was no effect of in-hospital mortality between 0.9% saline and crystalloids, with high-certainty of evidence. While the prevention of acute kidney injury was also similar among both types of crystalloid, the evidence was of lower certainty and they suggest further research could provide more helpful information in drawing a conclusion.

Yunos NM , Kim IB , Bellomo R , et al. The biochemical effects of restricting chloride-rich fluids in intensive care. Crit Care Med. 2011;39:2419–2424.

Yunos NM , Bellomo R , Hegarty C , Story D , Ho L , Bailey M . Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308:1566–1572.

Raghunathan K , Shaw A , Nathanson B , et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med. 2014;42:1585–1591.

Rochwerg B , Alhazzani W , Sindi A , et al. Fluid resuscitation in sepsis: a systematic review and network meta-analy-sis. Ann Intern Med. 2014;161:347–355.

Shaw AD , Raghunathan K , Peyerl FW , Munson SH , Paluszkiewics SM , Schermer CR . Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med. 2014;40:1897–1905.

Shaw AD , Bagshaw SM , Goldstein SL , et al. Major complications, mortality, and resource utilization after open abdominal surgery: 09% saline compared to Plasma-Lyte. Ann Surg. 2012;255:821–829.

Young P , Bailey M , Beasley R , et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314:1701–1710.

Semler NW , Wanderer JP , Ehrenfeld JM , et al. Balanced crystalloids versus saline in the intensive care unit: the SALT randomized trial. AM J Respir Crit Care Med. 2017;195:1362–1372.

Continuous versus Intermittent Renal Replacement Therapy

Hoste EA , et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med*. 2015;41(8):1411–1423.

This cross-sectional study examined the incidence of AKI by examining over 1800 patients at 97 different medical centers from 33 different countries during the first week of ICU admission. Over 57% of patients developed AKI, with 18.4%, 8.9%, and 30.0% developing KDIGO stage 1, 2, and 3 AKI, respectively. Of the patients who developed AKI, 23.5% required renal replacement therapy during their first week in the ICU. The risk of death increased with greater severity of AKI and patients with stage 3 AKI had a greater than 7-fold increased risk of death compared to ICU patients without AKI. This study highlights the high burden and morbidity of AKI in critically ill patients.

Davenport A . Renal replacement therapy in the patient with acute brain injury. *Am J Kidney Dis*. 2001;37(3):457–466.

This review covers the best practices in managing renal replacement for patients with acute neurologic injury. Conventional HD can lower cerebral perfusion pressure both through a reduction in mean arterial pressure as well as an increase in cerebral edema due to osmotic shifts from rapid solute removal. CRRT is the preferred modality for patients with acute neurologic injury who are at risk for cerebral edema. Peritoneal dialysis also allows for slow solute removal and has minimal effects on intracranial pressure, however this therapy is more challenging to initiate in critically ill patients.

Davenport A . The clinical application of CRRT—current status: continuous renal replacement therapies in patients with liver disease. *Sem Dialysis*. 2009;22(2):169–172.

Patients with both acute and chronic liver failure present a challenge when the need for RRT arises. They are often hypotensive due to high levels of nitric oxide and other endogenous vasodilators. Patients with fulminant liver failure often have elevated ammonia levels and are at risk for increased intracranial pressure with IHD. Similar to patients with neurologic injury, this is due both to decreased mean arterial pressure as well as rapid lowering of the serum osmolality and osmotic movement of water into brain tissue. CRRT is preferred for patients with fulminant liver failure or severe hyperammonemia.

Augustine JJ , et al. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis*. 2004;44(6):1000–1007.

Eighty critically ill patients with AKI and a requirement for RRT were randomized to either IHD or continuous venovenous hemodialysis (CVVHD). The IHD group received thrice weekly dialysis with standard blood and dialysis flow rates of 300 and 500 mL/min, respectively. Patients in the CVVHD group had greater volume removal and less hypotension than patients in the IHD group, however this did not translate to an improvement in clinical outcomes. There was no difference for in-hospital mortality or recovery of renal function when comparing IHD to CVVHD.

Lins RL , et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. *Nephrol Dialysis Transplant*. 2009;24(2):512–518.

This was a multicenter RCT of 316 critically ill patients with AKI who developed a need for RRT and were randomized to continuous venovenous hemofiltration (CVVH) or IHD. The IHD group in this study received treatments that more closely resembled SLED—daily hemodialysis with low blood and dialysate flows, and a long duration of 4–6 hours. There was no difference in the outcomes of in-hospital mortality, ICU, or hospital length of stay, or renal function at follow-up. There were also no differences in mortality when examining pre-specified subgroups including patients with sepsis, elderly patients (over 70 years old), or patients requiring mechanical ventilation.

Uehlinger DE , et al. Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dialysis Transplant*. 2005;20(8):1630–1637.

This single center trial randomized 125 critically ill patients with AKI requiring RRT to either continuous venovenous hemodiafiltration (CVVHDF) or IHD. The patients in the IHD group received standard intensite treatments over 3 to 4 hours as deemed appropriate by the treating nephrologist, however the median number of IHD treatments was high at 5 per week. There were no differences for in-hospital mortality, hospital length of stay, or duration of RRT when comparing CVVHDF to IHD.

Mehta RL , et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int*. 2001;60(3):1154–1163.

A multicenter trial (four medical centers in California) which randomized 166 ICU patients with AKI requiring RRT to either IHD or continuous renal replacement therapy. Notably some of the patients in the CRRT group received continuous arteriovenous hemodiafiltration (CAVHDF) and some received continuous venovenous hemodiafiltration (CVVHDF). This was the only major trial of CRRT vs. IHD which showed a significant difference between the two groups: in-hospital mortality was 65.5% in the CRRT group and 47.6% in the IHD group. Part of this difference appears to be due to unequal randomization of patients with severe illness between the two groups. In the CRRT group, 42.9% had liver failure compared to 29.3% in the IHD group. The APACHE III score was also higher in the CRRT group. Both of these differences were statistically significant and would be expected to affect mortality, independent of the assigned RRT modality.

Palevsky PM , et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359(1):0–72.

This study's aim was to assess whether the intensity of RRT affected outcomes for critically ill patients with AKI. At 27 hospitals there were 1124 patients randomized to high intensity (IHD/SLED 6 days per week or CVVHDF with an effluent rate of 35 mL/kg/h) or low intensity RRT (IHD/SLED 3 days per week or CVVHDF with an effluent rate of 20 mL/kg/h). There was no difference in the primary endpoint of 60-day mortality: 53.6% in the high intensity group and 51.5% in the low-intensity group. There were higher rates of hypotension and electrolyte disturbances in the high-intensity group. This study does not support the use of higher intensity RRT.

Evanson JA , et al. Prescribed versus delivered dialysis in acute renal failure patients. *Am J Kidney Dis*. 1998;32(5):731–738.
This study assessed the prescribed vs. delivered dose of dialysis in 40 hospitalized patients who experienced AKI requiring IHD. Forty-nine percent of the patients were prescribed a dialysis treatment which was below the guideline-recommended minimum adequate dose (a Kt/V of 1.2). Additionally, 68% of patients had an inadequate delivered dose of IHD. This study highlights the difference between prescribed and delivered dose of IHD in hospitalized patients with AKI, and also emphasizes the frequency of inadequate dialysis prescriptions.

Colloid versus Crystalloids

Annane D , Siami S , Jaber S , et al. Effects of fluid resuscitation with colloids vs. crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA* 2013;310:17–1809. PMID 24108515
The investigators performed a randomized, multicenter clinical trial stratified by case mix on 2857 patients admitted to one of 57 ICUs. Patients were randomized to receive either colloids or crystalloids. There was no difference in mortality at day 28 (primary outcome); however, survival was higher in the colloid group by day 90. There was no difference in the need for renal replacement therapy. Days alive without mechanical ventilation or vasopressor therapy at days 7 and 28 were greater in the colloid group. The authors concluded their results should be considered preliminary.
Finfer S , Bellomo R , Boyce N , et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:56–2247. PMID 15163774
The investigators conducted a randomized, multicenter, double-blind trial to determine the effect of either 4% albumin or NS on mortality of ICU patients who needed fluid resuscitation. There was no difference in 28-day mortality between patients (n = 3497) who received albumin compared to those (3500) who received NS. Furthermore, there was no difference organ failure, ICU or hospital length of stay, duration of mechanical ventilation or renal replacement therapy.
Gattas DJ , Dan A , Myburgh J . Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systemic review of effects on mortality and treatment with renal replacement therapy. *Intensive Care Med*. 2013;39:68–558. PMID 23423413
Two meta-analyses demonstrate that resuscitation with HES is associated with the need for RRT. Moreover, mortality is higher when HES is used although in one study, the statistical significance is borderline.
Gomez H , Priyanka P , Bataineh A , et al. Effects of 5% albumin plus saline versus saline alone on outcomes from large-volume resuscitation in critically ill patients. *Crit Care Med*. 2021;49:79–90. PMID 33165027.
Using two ICU databases that covered 14.5 years, the authors performed a retrospective cohort study evaluating the effects of 5% albumin plus NS versus NS on outcomes in critically ill patients. Albumin treated patients had lower mortality rates at 30, 90, and 365 days. There was a higher risk of acute kidney in the albumin group that did not result in chronic renal insufficiency.
Mandell J , Palevsky PM . Treatment of severe hypovolemia or hypovolemic shock in adults. In: www.uptodate.com. Accessed 2/3/2021
Contemporary review of the approach to the treatment of patients with hypovolemia.
Martin AMA , Mendoza JAB , Muriel A , et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. *Cochrane Database Syst Rev*. 2019;7:CD012247. PMID 31334842
The authors performed a meta-analysis evaluating the effect of BSS versus NS on hospital mortality and acute kidney injury (AKI). Twenty-one randomized controlled trials with a total of 19,054 patients were used. No difference between BSS and NS in either outcome variable was observed. The certainty of evidence for mortality was high, whereas it was low for AKI.
Myburgh JA , Finfer S , Bellomo R , et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:11–1901. PMID 23075127

The authors randomly assigned ICU patients (n = 7000) to either 6% hydroxyethyl starch (HES) or NS for fluid resuscitation. There was no significant difference in mortality at 90 days (primary outcome). Although more patients in the NS group had evidence of kidney injury, more patients in the HES group required renal replacement therapy (RRT).

Perner A , Haase N , Guttormsen AB , et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367:34–124. PMID 22738085

The investigators performed a randomized, multicenter, blinded, parallel-group study evaluating treatment of either 6% HES 130/0.42 or Ringer's acetate (RA) in patients (n = 804) with severe sepsis. Ninety-day mortality and need for RRT were greater in the HES-treated patients.

Semler MW , Self WH , Wanderer JP , et al. Balanced crystalloids versus saline in critically ill adults. *N Eng J Med*. 2018;378:39–829. PMID: 29485925

A pragmatic, cluster randomized, multiple-crossover trial was conducted in five intensive care units. Patients (n = 15,802) were treated with normal saline or balanced salt solutions (LR and Plasma-Lyte-A [PLA]) based on a randomization scheme according to which unit the patient was admitted. Patients in the balanced salt solution (BSS) group had fewer major adverse kidney events than the NS group. There was a trend towards lower need for renal replacement therapy and 30-day mortality BSS group. There was no difference in persistent kidney dysfunction.

The SAFE study investigators . Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357:84–874. PMID 17761591

The authors performed a post-hoc analysis of patients with traumatic brain injury who had been enrolled in the SAFE study (n = 6890). Of those patients with a Glasgow Coma Scale of <9 who received albumin, 41.8% died. The corresponding death rate in the saline group was 22.2%.

Zarychanski R , Abou-Setta AM , Turgeon AF , et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. *JAMA* . 2013;309:88–678. PMID 23407978

Gastrointestinal Bleeding

Chan FK , Wong VW , Suen BY , et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet* . 2007;369:6–1621. 28

*Four-hundred-forty-one patients who were taking non-selective NSAIDs and had a history of hospital admission for upper-gastrointestinal bleeding (*H. pylori *negative) were randomized to receive either celecoxib and placebo or celecoxib and esomeprazol. Patients were then followed for 12 months, with the primary endpoint being recurrent ulcer bleeding. Combination treatment was more effective than celecoxib alone for prevention of ulcer bleeding in patients at high risk.*

Cook D , Guyatt G , Marshall J , et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med*. 1998;338:1–779. 21

In this multi-center, randomized, blinded, placebo-controlled trial, members of the Canadian Critical Care Trials Group compared sucralfate with the H2-receptor antagonist ranitidine for the prevention of UGIB. Twelve hundred critically ill patients on mechanical ventilation were enrolled, and those who received ranitidine had a significantly lower rate of clinically relevant gastrointestinal bleeding. There were no significant differences in the rates of ventilator-associated pneumonia, the duration of the stay in the ICU, or mortality.

Graham DY , Lew GM , Evans DG , Evans DJ , Klein PD. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. A randomized controlled trial.” *Ann Intern Med*. 1991 August;115(4):6–926. 82

In this study of 105 VA patients with UGI ulcers, patients were randomized to receive either ranitidine or ranitidine plus “triple therapy” (tetracycline, metronidazole, bismuth

subsalicylate). “Triple therapy” was administered for the first 2 weeks of ulcer treatment only. Patients then underwent endoscopy after 2, 4, 8, 12, and 16 weeks of therapy. “Triple therapy” was superior to ranitidine alone for duodenal ulcer healing, as evidenced by more rapid ulcer healing on endoscopy.

Groszmann RJ , Garcia-Tsao G , Bosch J , et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med*. 2005;353:61–2254. 47

Nonselective beta-adrenergic blockers are known to decrease portal pressure, but their effectiveness in preventing varices was unknown at the time of this study. Two-hundred-thirteen patients with cirrhosis and portal hypertension were randomly assigned to beta-blocker or placebo, with the primary end point being the development of gastroesophageal varices or variceal hemorrhage. There were no significant differences in the rates of variceal bleeds, nor were there significant differences in the rates of ascites, encephalopathy, liver transplantation, or death. Adverse events were more common among patients in the beta-blocker group than among those in the placebo group.

Hwang SJ , Lin HC , Chang CF , et al. A randomized controlled trial comparing octreotide and vasopressin in the control of acute esophageal variceal bleeding. *J Hepatol*. 1992;16:0–532. 49

This randomized controlled trial was conducted to compare the efficacy of intravenous infusion of octreotide with vasopressin. Forty-eight cirrhotic patients with endoscopically proven bleeding esophageal varices were randomized to one of the two treatment arms. Octreotide infusion was more effective, and had fewer side effects, than vasopressin in initially controlling acute esophageal variceal bleeding, until definitive treatment (endoscopic sclerotherapy) could be performed.

Jensen D , Mahicado G , et al. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. *N Engl J Med*. 2010;342(2):78–82. 83

One-hundred-twenty-one patients were enrolled in this study examining the role of colonoscopy in patients with hematochezia and diverticulosis. One fifth of patients had definitive diverticular hemorrhage; colonoscopic intervention prevented the need for surgical intervention.

Khuroo MS , Yattoo GN , Javid G , et al. A comparison of omeprazole and placebo for bleeding peptic ulcer. *N Engl J Med*. 1997;336:8–1054. 35

The role of medical treatment for patients with bleeding peptic ulcers was uncertain at the time of this double-blind, placebo-controlled trial. Two-hundred-twenty patients with duodenal, gastric or stomal ulcers, and signs of recent bleeding, confirmed by endoscopy, were enrolled and randomly assigned to receive 5 days of omeprazole or placebo. The outcome measures studied were further bleeding, surgery, and death. Treatment with omeprazole decreased the rate of further bleeding and the need for surgery.

Laine L , Shah A. Randomized eternal of urgent vs. elective colonoscopy in patient hospitalized with lower GI bleeding. *Am J Gastroenterol.* 2010;105:41–2636.

Eighty-five eligible patients had urgent upper endoscopy; 13 (15%) had an upper source. The remaining 72 were randomized to urgent or elective colonoscopy. There was no significant difference between the two groups in further bleeding, units of blood transfused, hospital days, subsequent diagnostic or therapeutic interventions, and hospital charges. Note that this study was limited by its failure to reach the pre-specified sample size. The authors conclude that patients with clinically serious hematochezia should have upper endoscopy initially to rule out an upper GI source, and that there was no difference between urgent colonoscopy and routine elective colonoscopy.

Lau JY , Sung JJ , Lam YH , et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. *N Engl J Med*. 1999;340:1–675. 18

In this prospective, randomized study, the authors compared endoscopic re-treatment with surgery after initial endoscopy for control of bleeding peptic ulcers. Endoscopic re-treatment reduced the need for surgery without increasing the risk of death. Endoscopic therapy was also associated with fewer complications than surgery .

Lau J , Yu Y , Tang R , et al. Timing of endoscopy for acute upper gastrointestinal bleeding. *N Engl J Med*. 2020;382:1299–1308. 16

In this single center, randomized, patients presenting to the ER underwent UGI endoscopy within 6 hours of admission (urgent endoscopy group) or 6–24 hours after admission (delay-endoscopy group). Note that the patients were screened using the Glasgow-Batchford scoring system, and thus the patients who were enrolled were at high risk for bleeding or death. Patients who were in hypotensive shock were excluded. 516 patients were enrolled, and there was no difference between groups with respect to mortality, further bleeding episodes within 30 days, or the presence of ulcers, but the rate of endoscopic hemostatic treatments was higher in the urgent-endoscopy group. The authors conclude that there was no difference in mortality between endoscopy before 6 hours, or between 6–24 hours after admission.

Poultsides GA , Kim CJ , Orlando R, 3rd , Peros G , Hallisey MJ , Vignati PV. Angiographic embolization for gastroduodenal hemorrhage: safety, efficacy, and predictors of outcome. *Arch Surg*. 2008;143:61–457. 71

Fifty-seven patients were referred to a tertiary referral center for management after failed endoscopic treatment of UGIB. Surgery was not immediately considered in these patients because of poor surgical risk, patient refusal to consent, or endoscopist's decision. Angiographic embolization for gastroduodenal hemorrhage was associated with in-hospital re-bleeding in almost half of these patients. Angiographic failure was associated with delay to embolization, blood transfusion of more than 6 units of packed red blood cells, or re-hemorrhage from a previously suture-ligated duodenal ulcer.

Sarin SK , Lamba GS , Kumar M , Misra A , Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med*. 1999;340:93–988. 55

The authors compared propranolol therapy and endoscopic ligation for the primary prevention of bleeding from esophageal varices. This prospective, controlled trial enrolled patients who had large varices (>5 mm in diameter) that were considered to be at high risk for bleeding. The patients were assigned to either propranolol therapy or weekly variceal ligation. After 18 months, the probability of bleeding was 43% in the propranolol group and 15% in the ligation group. Endoscopic ligation of the varices was proven to be safe and more effective than propranolol for the primary prevention of variceal bleeding.

Villanueva C , Minana J , Ortiz J , et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med*. 2001;345:55–647. 56

One-hundred-forty-four patients with cirrhosis who were hospitalized with esophageal variceal bleeding were randomized to receive treatment with endoscopic ligation or the medical therapy with nadolol and isosorbide mononitrate. Ligation sessions were repeated every two to three weeks until the varices were eradicated. The primary end points were recurrent bleeding, complications, and death. Combined therapy with nadolol and isosorbide mononitrate was more effective in preventing recurrent hemorrhage than endoscopic ligation, and was associated with a lower rate of major complications.

Acute Pancreatitis

Bakker OJ , et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med* . 2014;371(21):1983–1993.

In this randomized controlled trial, the authors compared the outcomes of an early (within 24 hours of randomization) naso-enteric tube feeding to the outcomes of an oral diet initiated 72 hours after presentation, and found that opposite to the popular belief, naso-enteric tube feeding has no additive benefit over oral feeding in reducing the rate of infection or death in patients with AP who are at a high risk of complications.

Chang L , et al. Preoperative versus postoperative endoscopic retrograde cholangiopancreatography in mild to moderate gallstone pancreatitis: a prospective randomized trial. *Ann Surg*. 2000;231(1):82–87.

A randomized control trial was conducted on patients with mild to moderate biliary pancreatitis to see whether pre-operative ERCP has an advantage over selective

postoperative ERCP. It was concluded that in cases with mild to moderate pancreatitis without concomitant cholangitis, postoperative ERCP does not only reduce the LOS and total cost of treatment, but it also decreases unnecessary ERCPs that would otherwise be performed preoperatively.

Da Costa DW , et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet* . 2015;386(10000):1261–1268.

In this multicenter, parallel-group, assessor-masked, randomized controlled trial, the authors investigated the optimal timing of cholecystectomy for mild biliary pancreatitis. Same-admission cholecystectomy was associated with significantly lower risk of mortality and biliary complications (same-admission vs. interval cholecystectomy; 5% vs. 17%, p=0.002). The risk of recurrent pancreatitis and biliary colic was also significantly lower with same-admission cholecystectomy.

Dellinger EP , et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Ann Surg*. 2007;245(5):674–683.

The authors conducted a double-blinded, randomized, placebo-controlled trial to study the role of antibiotic treatment and prophylaxis in 100 patients with clinically severe acute necrotizing pancreatitis. The study was conducted at 32 centers in North America and Europe. It was concluded that treatment with meropenem does not confer an advantage over placebo in reducing the risk of developing pancreatic or peri-pancreatic infections, mortality or requirement of surgical intervention. It was also concluded that there is no benefit of antibiotic prophylaxis in patients with acute necrotizing pancreatitis.

Lankisch PG. Treatment of acute pancreatitis: an attempted historical review. *Pancreatology* . 2010;10(2-3):134–141. doi:10.1159/000255465

This article is a fine attempt at a historical review on treatment of acute pancreatitis. It sheds light on how the past research impacts our current understanding of the topic. The author utilizes the well-known online medical libraries and their personal library collected over a period of 40 years as a pancreatologist to produce this excellent report.

Papachristou GI, Muddana V, Yadav D, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol*. 2010;105(2):435–441; quiz 442. doi:10.1038/ajg.2009.622

The authors perform a detailed comparison of various prognostic scoring systems for AP, including the more recent BISAP score. They deduce that BISAP score is reliable and easier to use because it has lesser components, however, it doesn't improve the predictive accuracy when compared to the conventional scoring systems like APACHE II and Ranson's score. The study puts emphasis on the need of devising novel models of scoring to improve the accuracy of predicting the severity of AP.

Sarr MG. 2012 revision of the Atlanta classification of acute pancreatitis. *Pol Arch Med Wewn* . 2013;123(3):118–124.

An excellent account on the revised Atlanta classification of acute pancreatitis that features the changes from the older classification.

Tenner S , et al.. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013;108(9):1400–1415; 1416.

ACG guidelines on the management of patients with AP. These guidelines take into account the recent advances and development in the understanding of diagnosis, etiology, and management of AP.

Yadav D , Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* . 2013;144(6):1252–1261. doi:10.1053/j.gastro.2013.01.068

The authors detail the descriptive epidemiology of pancreatic disease demonstrating the incidence, prevalence, and trends of acute pancreatitis with respect to patient demographics. The authors also elucidate the etiology of acute pancreatitis and provide an insight on disease progression and mortality.

Landmark Article of the 21st Century

A STEP-UP APPROACH OR OPEN NECROSECTOMY for NECROTIZING PANCREATITIS

Vansantvoort HC et al., *N Engl J Med* . 2010;362:1491–1502

Commentary by van Santvoort Hjalmar C.

Around 30% of patients with necrotizing pancreatitis develop secondary bacterial infection of the pancreatic and peripancreatic necrosis [1]. Infected necrosis causes sepsis with associated multiple-organ failure and is therefore an indication for invasive intervention [2]. The historical treatment was primary open necrosectomy: a laparotomy with complete debridement of the infected necrosis. Open necrosectomy was associated with a high risk of complications (34%–95%) and death (11%–39%) [3 , 4]. The alternative “step-up approach” aims at reducing the pro-inflammatory response of major surgery by control of the source of infection, rather than complete removal of the infected necrosis. The first step is percutaneous or endoscopic catheter drainage to mitigate sepsis; this may postpone or even obviate surgical necrosectomy. If drainage does not lead to clinical improvement, the next step is video-assisted retroperitoneal debridement (VARD) [5].

In the 2010 PANTER trial, 88 patients from 19 hospitals of the Dutch Pancreatitis Study Group with (suspected) infected necrotizing pancreatitis were randomized to primary open necrosectomy ($n = 45$) or the step-up approach ($n = 43$) [6]. The step-up approach reduced the primary end point of major complications (i.e., multiple-organ failure, bleeding, enteric perforations) and death (69% vs. 40%, $p = 0.006$). Of the patients assigned to the step-up approach, 35% were treated with catheter drainage only. Patients assigned to the step-up approach also had a lower rate of incisional hernias (7% vs. 24%, $p = 0.03$) and new-onset diabetes (16% vs. 38%, $p = 0.02$).

Patients with infected necrotizing pancreatitis should be treated with a step-up approach, consisting of catheter drainage, followed, if necessary, by minimally invasive necrosectomy.

van Santvoort HC, Bakker OJ, Bollen TL, et al. Dutch Pancreatitis Study Group. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* . 2011;141(4):1254–1263.

APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* . 2013;13(4):e1–e15.

Beger HG, Buchler M, Bittner R, Oettinger W, Block S, Nevalainen T, et al. Necrosectomy and postoperative local lavage in patients with necrotizing pancreatitis: results of a prospective clinical trial. *World J Surg*. 1988;12:255–262.

Traverso LW , Kozarek RA. Pancreatic necrosectomy: definitions and technique. *J Gastrointest Surg*. 2005;9:436–439.

Horvath KD, Kao LS, Ali A, Wherry KL, Pellegrini CA, Sinanan MN ,n et al. Laparoscopic assisted percutaneous drainage of infected pancreatic necrosis. *Surg Endosc*. 2001;15(7):677–682.

van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010;362(16):1491–1502.

Abdominal Compartment Syndrome

Kirkpatrick AW , Roberts DJ , De Waele J , et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*.2013; 39:1190–1206.

The second consensus conference report and expert panel on IAH and ACS by the WSACS. This report expands and updates on the 2006 WSACS consensus publication on IAH and ACS. The report uses the GRADE system to rate the quality of evidence and strength of management recommendations.

Hecker A , Hecker B , Hecker M , et al. Acute abdominal compartment syndrome: current and therapeutic options. *Langenbecks Arch Surg*.2016;401:15–24.

Recent review of current diagnostic and therapeutic options of IAH, ACS and open abdomen.

Cheatham ML , White M , Sagraves S , Johnson J , Block E. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. *J Trauma Acute Care Surg*.2000; 49(4):621–627.

Study using APP as a parameter to monitor the clinical effects of IAH.

Sosa G , Gandham N , Landeras V , Calimag AP , Lerma E. Abdominal compartment ayndrome. *Disease-a-Month*.2019; 65.
Good overall review of ACS with a brief mention of historical milestones.
Kron IL , Harman PK , Nolan SP. The measurement of intrabdominal pressure as a criterion for abdominal re-exploration. *Ann Surg*. 1984;199:28–30.
The paper was the first to describe abdominal compartment syndrome and described a technique how to measure intra-abdominal pressure.
Fietsam J , Villalba M , Glover J , Clark K. Intra-abdominal compartment syndrome as a complication of ruptured abdominal aorta aneurysm repair. *Am Surg*. 1989:55(6):396–402.
First to introduce the term intra-abdominal compartment syndrome.
An G , West MA. Abdominal compartment syndrome: a concise clinical review. *Crit Care Med* . 2008;36(4):1304–1310.
A concise review of ACS.
Carr JA. Abdominal compartment syndrome: a decade of progress. *J Am Coll Surg*. 2013;216:135–146.
Another good review of ACS.
Cheatham ML. Abdominal compartment syndrome: pathophysiology and definitions. *Scand J Trauma Resusc Emerg Med*. 2009;17(1):10.
Another good physiologic review of ACS.
Hong JJ , Cohn SM , Perez JM , Dolich DO , Brown M , McKenney MG. Prospective study of the incidence and outcome of intra-abdominal hypertension and the abdominal compartment syndrome. *Brit J Surg.* 2002;89:591–596.
Prospective study to describe a low incidence of IAH/ACS in trauma patients.
Meldrum DR, Moore FA , Moore EE , Franciose RJ , Sauaia A , Burch JM. Prospective characterization and selective management of the abdominal compartment syndrome. *Am J Surg*. 1997;174:667–672.
Prospective study identifying trauma patients with ACS and their treatment.

Mesenteric Ischemia

Acosta S, Ögren M, Sternby N-H, Bergqvist D, Björck M. Clinical implications for the management of acute thromboembolic occlusion of the superior mesenteric artery: autopsy findings in 213 patients. *Ann Surg*. 2005; 241(3):516.
A study of 213 cases of acute thromboembolic occlusion of the SMA and intestinal infarction. Clinical suspicion of intestinal ischemia was documented in about one third of patients. The embolus/thrombus ratio was 1.4 to 1. Thrombotic occlusions were located more proximally than embolic occlusions and associated with more extensive intestinal infarction.
Becquemin J. Management of the diseases of mesenteric arteries and veins: clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* . 2017; 53(4):455–457.
Sixty-four recommendations from the European Society for Vascular Surgery (ESVS) guidelines committee regarding the management of acute and chronic arterial ischemia, nonocclusive mesenteric ischemia, visceral aneurysms, and dissection.
Björck M , et al. Revascularization of the superior mesenteric artery after acute thromboembolic occlusion. *Brit J Surg*. 2002;89(7):923–927.
Sixty patients with acute thromboembolic occlusion of the SMA undergoing revascularization procedures across 21 Swedish hospitals. Fifty-eight patients had an exploratory laparotomy and subsequent revascularization, and two were treated with thrombolysis alone. Mortality rates were 43% at 30 days and 67% at 5 years.
Cho J-S , et al. Long-term outcome after mesenteric artery reconstruction: a 37-year experience. *J Vasc Surg*. 2002; 35(3):453–460.
A retrospective review of 48 consecutive patients who underwent revascularization for acute mesenteric ischemia (AMI) of nonembolic origin. Perioperative (<30 days) mortality rate was 52%. Major complications occurred in 60% of the cases. The late survival rates were 54%

and 20% at 5 and 10 years,

Clair DG, Beach JM. Mesenteric ischemia. *N Engl J Med*. 2016; 374(10):959–968.

A review article that explains the pathophysiology, diagnosis, and treatment of intestinal ischemic syndromes.

Corcos O , et al. Effects of a multimodal management strategy for acute mesenteric ischemia on survival and intestinal failure. *Clin Gastroenterol Hepatol*. 2013; 11(2):158–165. e152.

A pilot study demonstrating that a multimodal management team approach of 18 consecutive patients with occlusive AMI achieved a survival rate of 95% at 30 days and 89% at 2 years.

Johnston KW , et al. Mesenteric arterial bypass grafts: early and late results and suggested surgical approach for chronic and acute mesenteric ischemia. *Surgery*. 1995; 118(1):1–7.

A study of 34 patients who underwent mesenteric vascular graft placement for chronic and acute mesenteric ischemia. Of the patients who underwent only a single SMA or celiac bypass, two of five died of bowel infarction; only one of 16 patients who underwent both celiac and SMA bypass had to undergo a repeat surgical procedure because of graft occlusion. Complete revascularization of the SMA and celiac artery or pelvis or both and prograde bypass may reduce the risk of late bowel ischemia.

Kim AY, Ha HK. Evaluation of suspected mesenteric ischemia: efficacy of radiologic studies. *Radiologic Clin*. 2003; 41(2):327–342.

A review article that studies the reports the utility of radiographic diagnostic studies in patients with suspected mesenteric ischemia.

Klempnauer J , et al. Long-term results after surgery for acute mesenteric ischemia. *Surgery* . 1997;121(3):239–243.

Ninety patients with acute mesenteric ischemia treated by vascular reconstruction or bowel resection, or both, between 1972 and 1993 were studied. The overall mortality was 66%. In the 31 patients who were discharged from the hospital, the 2- and 5-year survival rates were 70% and 50%.

Lim S , et al. Contemporary management of acute mesenteric ischemia in the endovascular era. *Vasc Endovasc Surg*. 2019;53(1):42–50.

A review article that supports an endovascular first approach in the management of patients with AMI, citing evidence that this strategy may have improved outcomes in the immediate postoperative period.

Mamode N , et al. Failure to improve outcome in acute mesenteric ischaemia: seven year review. *Eur J Surg*. 1999;165(3):203–208.

A study of 57 patients presenting with acute mesenteric ischemia. Only 18 (32%) patients were accurately diagnosed before operation or death. Forty-six of the 57 patients died.

Milner R , et al. Superior mesenteric artery angioplasty and stenting via a retrograde approach in a patient with bowel ischemia: a case report. *Vasc Endovasc Surg*. 2004;38(1):89–91.

This study reports a novel combination of open and endovascular techniques via a retrograde superior mesenteric artery (SMA) approach to treat acute mesenteric ischemia in the setting of an acute abdomen.

Roussel A , et al. Revascularization of acute mesenteric ischemia after creation of a dedicated multidisciplinary center. *J Vasc Surg*. 2015;62(5):1251–1256.

A study of 83 patients with AMI, 29 of whom underwent revascularization. Overall 2-year survival was 89.2%, and 30-day operative mortality was 6.9%. The 2-year primary patency rate of open revascularization was 88%.

Ryer EJ , et al. Revascularization for acute mesenteric ischemia. *J Vasc Surg*. 2012;55(6):1682–1689.

A study of 93 patients with AMI who underwent emergency arterial revascularization. Forty-five patients were treated during the 1990s and 48 during the 2000s. Patient demographics and risk factors were similar and etiology remained constant between the groups with in situ thrombosis being the most common followed by arterial embolus. Thirty-day mortality was 27% in the 1990s and 17% during the 2000s (p = 0.28). Major adverse events occurred in 47% of patients with no difference between decades. There was no significant difference in outcomes between open and endovascular revascularization.

Schoots I , et al. Systematic review of survival after acute mesenteric ischaemia according to disease aetiology. *Brit J Surg*. 2004;91(1):17–27.

A review of 45 observational studies containing 3692 patients with acute mesenteric ischemia showed that the overall survival after acute mesenteric ischemia has improved over the past four decades. Surgical treatment of arterial embolism has improved outcome whereas the mortality rate following surgery for arterial thrombosis and non-occlusive ischemia remains poor.

Wyers MC , et al. Retrograde mesenteric stenting during laparotomy for acute occlusive mesenteric ischemia. *J Vasc Surg*. 2007;45(2):269–275.

Three different revascularization methods used in 13 patients with arterial occlusive AMI. At 17%, the retrograde open stenting group had the lowest hospital mortality compared with bypass at 80% (p = 0.08) and percutaneous stent at 100% (p = 0.11).

Treatment of Variceal Bleeding in Cirrhotic Patients

Sass DA , Chopra KB. Portal hypertension and variceal hemorrhage. *Med Clin North Am*. 2009;93(4):837–853.

This review article describes the classification system of portal hypertension and discusses the pathophysiology of varices and variceal hemorrhage. Authors report on the natural history of varices including the incidence of varices in patients with cirrhosis, the rate of development, and the yearly rate of variceal hemorrhage. They identify predictors of variceal hemorrhage.

de Franchis R ; Baveno V Faculty . Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015; 63:743–752.

The Baveno VI faculty provides an expert consensus statement that defines key events in portal hypertension, clarifies terminology, and standardizes language regarding variceal hemorrhage. The consensus statement issues evidence-based recommendations for conducting of clinical trials, including identification of 6 week mortality as the primary endpoint that should be used for studies on acute variceal bleeding. Authors report a 6 week mortality rate of 10–20% for variceal bleeding.

Villanueva C , Colomo A , Bosch A , et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368:11–21.

This randomized controlled trial enrolled 921 patients with acute upper gastrointestinal bleeding to evaluate restrictive versus liberal blood transfusion strategies. Red blood cell transfusion to a hemoglobin goal 7–9 g/dL was associated with a significant improvement in 6 week survival compared to a liberal tansfusion strategy to maintain hemoglobin of 9–11 g/dL (95% vs. 91%; p = 0.02). The subgroup analysis of patients with cirrhosis revealed significantly lower early rebleeding and mortality rates in patients randomized to restrictive PRBC transfusion.

Chavez-Tapia NC , Barrientos-Gutierrez T , Tellez-Avila F , et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. *Aliment Pharmacol Ther*. 2011;34(5):509–518.

In a meta-analysis of 12 trials including over 1200 patients with cirrhosis and GI bleeding, antibiotic prophylaxis was compared with either placebo or no intervention, and the benefit of antibiotic use was demonstrated with regard to mortality (relative risk [RR] 0.79, 95% CI 0.63–0.98), bacterial infections (RR 0.35, 95% CI 0.26–0.47), and rebleeding (RR 0.53, 95% CI 0.38–0.74).

Wells M , Chande N , Adams P , et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. *Aliment Pharmacol Ther*. 2012;35:1267–1278.

In a meta-analysis of 30 RCTs, authors report the use of vasoactive agents in acute variceal hemorrhage is associated with lower 7-day all-cause mortality (p = 0.02), improved control of acute hemorrhage (p <0.001), lower transfusion requirements (p <0.001), and shorter duration of hospitalization (p = 0.007).

Levacher S , Letoumelin P , Pateron D , Blaise M , Lapandry C , Pourriat JL. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* . 1995;346:865–868.

In a prospective, randomized, double-blind trial, cirrhosis patients with upper gastrointestinal hemorrhage were randomized to receive early initiation of an infusion of terlipressin and glyceryl trinitrate at their homes prior to transport to the hospital versus placebo. Authors report improved bleeding control and improved mortality in the intervention group.

Escorsell A , Pavel O , Cardenas A , et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: a multicenter randomized, controlled trial. *Hepatology* . 2016;63:1957–1967.

A randomized, controlled trial compared esophageal stent versus balloon tamponade to control variceal hemorrhage in 28 patients with cirrhosis and variceal hemorrhage. Success of therapy was defined as survival at day 15 with control of bleeding and without serious adverse events. The esophageal stent group showed significant improvement in success of therapy (66% vs. 20%; p = 0.025) and control of bleeding (85% vs. 47%; p = 0.037), with lower rates of serious adverse events (15% vs. 47%; p = 0.077).

Garcia-Tsao G , Abraldes JG , Berzigotti A , Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* . 2017;65(1):310–335.

The American Association for the Study of Liver Diseases provides updated, evidence-based guidance on risk stratification, diagnosis, and management of portal hypertension, varices, and variceal hemorrhage.

Tripathi D , Stanley AJ , Hayes PC , et al; U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* . 2015;64(11):1680–1704.

The Clinical Services and Standards Committee of the British Society of Gastroenterology provides updated guidelines on the management of variceal hemorrhage, specifically with regards to primary prophylaxis, acute variceal hemorrhage, and secondary prophylaxis. They attempt to standardize language by defining terms such as acute variceal bleeding, variceal re-bleeding, and clinically significant bleeding.

Thiele M , Krag A , Rohde U , Gluud LL. Meta-analysis: banding ligation and medical interventions for the prevention of rebleeding from oesophageal varices. *Aliment Pharmacol Ther*. 2012;35(10):1155–1165.

This meta-analysis includes 9 randomized clinical trials and 955 patients to assess the effectiveness of combination endoscopic variceal ligation and nonselective beta blockade versus monotherapy in preventing variceal rebleeding. Authors conclude that combination therapy reduces the risk of re-bleeding but not overall mortality.

García-Pagán JC , Caca K , Bureau C , et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med.* 2010;362(25):2370–2379.

Authors randomized 63 patients with cirrhosis and variceal bleeding who had been treated with vasoactive drugs and endoscopic therapy to receive early TIPS or continuation of pharmacotherapy only. Fourteen patients in the pharmacotherapy group met composite criteria for re-bleeding events versus 1 patient in the early-TIPS group (p <0.001). One year survival was 86% in the early-TIPS group as compared to 61% in the pharmacotherapy group (p <0.001).

Rikkers LF , Jin G. Emergency shunt. Role in the present management of variceal bleeding. *Arch Surg.* 1995;130(5):472–477.

This retrospective review of 42 patients treated with selective and nonselective emergency portosystemic shunt operations observed a mortality rate of 43% in patients with Child's class C cirrhosis.

Catheter-Related Infections

Sherertz RJ , Ely EW , Westbrook DM , et al. Education of physicians-in-training can decrease the risk for vascular catheter infection. *Ann Intern Med.* 2000;132(8):1–864.

A simple education program given to interns during the first week of their residency resulted in a decrease in catheter infections compared to historical infection rates.

Raad II , Hohn DC , Gilbreath BJ , et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp*

Epidemiol. 1994;15(4 Pt 1):1–823.
Catheter infection rates were reduced when the proceduralist used cap, mask, sterile gloves and gown, and a sterile drape covering the entire patient when inserting a central venous catheter.
Maki DG , Ringer M , Alvarado CJ. Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet*. 1991;338(8763):43–339.
Skin preparation with chlorhexidine was found to be superior to povidone-iodine in preventing catheter infection.
Raad I , Darouiche R , Dupuis J , et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. The Texas Medical Center Catheter Study Group. *Ann Intern Med*. 1997;127(4):74–267.
One of two seminal investigations demonstrating the use of an antibiotic impregnated catheter reduces CLABSIs.
Maki DG , Stolz SM , Wheeler S , Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter. A randomized, controlled trial. *Ann Intern Med*. 1997;127(4):66–257.
The second of two seminal investigations demonstrating the use of antiseptic catheters reduces CLABSIs.
Darouiche RO , Raad II , Heard SO , et al. A comparison of two antimicrobial-impregnated central venous catheters. Catheter Study Group. *N Engl J Med*. 1999;340(1):1–8.
Central venous catheters impregnated with minocycline and rifampin (external surface and lumen) were found to be superior in preventing CLABSIS compared to catheters impregnated with chlorhexidine and silver-sulfadiazine on the external surface.
Parienti JJ , Mongardon N , Megarbane B , et al. Intravascular complications of central venous catheterization by insertion site. *N Engl J Med*. 2015;373(13):9–1220.
The subclavian insertion site was associated with the lowers risk of infection compared to internal jugular and femoral sites. However, mechanical complications were higher.
Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med*. 2000;132(5):391–402.
A review of the state of the art in preventing catheter infections. Subsequent reviews a decade later (MMWR) demonstrated a significant decline in CLABSIs nationwide.
Berenholtz SM , Pronovost PJ , Lipsett PA , et al. Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med*. 2004;32(10):20–2014.
Use of a checklist and bundled approach to insertion of central venous catheters resulted in a sustained decrease in CLABSIs.
Pronovost P , Needham D , Berenholtz S , et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med*. 2006;355(26):32–2725.
Use of the protocol outlined in reference 9 was successfully implemented in Michigan ICUs.
Walz JM , Ellison RT, 3rd , Mack DA , et al. The bundle “plus”: the effect of a multidisciplinary team approach to eradicate central line-associated bloodstream infections. *Anesth Analg*. 2015;120(4):76–868.
Adding antimicrobial impregnated catheters and chlorhexidine dressings to the bundle and treating very CLABSI as a sentinel event resulted in sustained reductions in CLASBIs to 0.5–0.8/1000 catheter days.
Cartier V , Haenny A , Inan C , Walder B , Zingg W. No association between ultrasound-guided insertion of central venous catheters and bloodstream infection: a prospective observational study. *J Hosp Infect*. 2014;87(2):3–810.
Although use of the ultrasound during insertion of central venous catheters may prevent complications, CLABSIs do not appear to be reduced.
Zacharioudakis IM , Zervou FN , Arvanitis M , Ziakas PD , Mermel LA , Mylonakis E. Antimicrobial lock solutions as a method to prevent central line-associated bloodstream infections: a meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2014;59(12):9–1741.
Antimicrobial locks appear to be useful in preventing CLABSIs but the data are heavily weighted towards hemodialysis catheters.

Voor AF , Helder OK , Vos MC , et al. Antiseptic barrier cap effective in reducing central line-associated bloodstream infections: a systematic review and meta-analysis. *Int J Nurs Stud*. 2017;69:34–40.
Antiseptic barrier caps may be useful in preventing CLABSIs if the baseline rate is high.

Diagnosis and Prevention of Ventilator-Associated Pneumonia

Muscedere JG , Day A , Heyland DK. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. Clin Infect Dis. 2010; 51(Suppl 1):S120–5.
Muscedere J , Dodek P , Keenan S , Fowler R , Cook D , Heyland D. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: diagnosis and treatment. J Crit Care. 2008;23:47–138.
Muscedere J , Dodek P , Keenan S , Fowler R , Cook D , Heyland D. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. J Crit Care. 2008;23:37–126.
Sinuff T , Muscedere J , Cook DJ , et al.; Canadian Critical Care Trials G. Implementation of clinical practice guidelines for ventilator-associated pneumonia: a multicenter prospective study. Crit Care Med. 2013;41:15–23.
Scott IA , Harper CM. Guideline-discordant care in acute myocardial infarction: predictors and outcomes. Med J Aust. 2002;177:26–31.

Treatment of Ventilator-Associated Pneumonia

Lassen HCA. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen. *Lancet*. 1953;1:37.
This is an early description of the novel management of polio-related respiratory failure with tracheostomy and manual bag mask ventilation. The authors reported a 50% mortality reduction with this technique. This landmark finding laid the foundation for modern critical care.
Johanson WG , Pierce AK , Sanford JP. Changing pharyngeal bacterial flora of hospitalized patients. *N Engl J Med*. 1969;21:1137–1140.
One of the initial pieces of work noting the changes of oropharyngeal flora in hospitalized patients and identifying the endotracheal tube as a risk factor for nosocomial pneumonia.
Pugin J , Auckenthaler R , Mili N , et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic “blind” bronchoalveolar lavage fluid. *Am Rev Respir Dis.* 1991;143:1121–1129.
This case series identified the clinical criteria which correlated with positive cultures obtained from tracheal secretions. They used these criteria to develop a scoring system which ultimately became known as the Clinical Pulmonary Infection Score.
Vazquez Guillamet C , Kollef MH. Is zero ventilator-associated pneumonia achievable?: practical approaches to ventilator-associated pneumonia prevention. *Clin Chest Med*. 2018;39:809–822.
A systematic review of current VAP prevention strategies with a good summary of the available evidence.
Kalil AC , Metersky ML , Klompas M , et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61–e111.
These are the most recent guidelines from the Infectious Disease Society of America on the diagnosis and treatment of VAP. These guidelines largely agree with their European equivalent.

Catheter-Associated Urinary Tract Infection

Hooton TM , Bradley SF , Cardenas DD et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(5):625–663.

The authors of this paper present the 2009 guidelines for the diagnosis, prevention, and management of catheter-associated urinary tract infections as prepared by an Expert Panel of the Infectious Diseases Society of America. The paper outlines an approach for both asymptomatic and symptomatic urinary tract infections in the inpatient and long-term care settings.

Nicolle LE . Urinary catheter-associated infections. *Infect Dis Clin of North Am*. 2012;26 (1):13–27.

This paper presents a review of urinary catheter-associated infections including their epidemiology, pathophysiology, diagnosis, and treatment along with guidelines for use of catheters, maintenance, and infection-prevention strategies.

Gould CV , Umscheid CA , Agarwal RK , Kuntz G , Pegues DA . Healthcare Infection Control Practices Advisory Committee. Guideline for prevention of catheter-associated urinary tract infections 2009. *Infect Control Hosp Epidemiol*. 2010;31(4):319–326.

Published in 2010, this paper proposed guideline updates and expansions on the CDC Guideline for Prevention of Catheter-Associated Urinary Tract Infections. It reviewed questions and evidence addressing patient populations who should receive urinary catheters and approaches to best practices.

Kizilbash QF , Petersen NJ , Chen GJ , Naik AD , Trautner BW . Bacteremia and mortality with urinary catheter-associated bacteriuria. *Infect Control Hosp Epidemiol*. 2013 Nov;34(11):1153–1159. doi: 10.1086/673456.

The authors performed a retrospective cohort study that looked at bacteriuria, bacteremia, and associated mortality. Additionally, they looked at the effect of antimicrobial treatment of bacteriuria. Their study revealed that bacteremia due to a urinary source occurred infrequently, and that CAUTI was more associated with bacteremia than CAABU, but CAUTI and CAABU were not associated with mortality. They also found that antimicrobial therapy did not affect the outcomes.

Tambyah PA , Maki DG . Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1497 catheterized patients. *Arch Intern Med*. 2000 Mar 13;160(5):678–682. doi: 10.1001/archinte.160.5.678.

https://www.cdc.gov/infectioncontrol/guidelines/cauti/background.html

The authors designed a study to look at the clinical features of catheter-associated urinary tract infections with a focus on fever, symptomatic infection, and peripheral leukocytosis as measured outcomes. The study evaluated 1497 newly catheterized patients and concluded that CAUTIs are infrequently symptomatic or not a common cause of bloodstream infection. They are an important source of antibiotic-resistant organisms. Additionally, fever and leukocytosis are not good predictors in the diagnosis of CAUTI.

This CDC website outlines the definition, epidemiology, pathophysiology, and microbiology of catheter-associated urinary tract infections.

6. Mullin K, Kovacs C, Fatica C, et al. A multifaceted approach to reduction of catheter-associated urinary tract infections in the intensive care unit with an emphasis on “Stewardship of Culturing”. *Infect Control Hosp Epidemiol*. 2017;38(2):186–188. doi:10.1017/ice.2016.266.

The paper described a successful multimodal approach to limiting CAUTIs in ICUs, in a single institution, with protocols directed at placement, maintenance and removal of catheters combined with a stewardship approach to obtaining urine cultures.

7.Nicolle, LE. Catheter associated urinary tract infections. *Antimicrob Resist Infect Control*. 2014;3:23. doi: 10.1186/2047-2994-3-23.

The author reviewed catheter-associated urinary tract infections (CAUTIs) and the related spectrum of illness and morbidity. The importance of hospital and facility infection-control programs to monitor use and maintenance of urinary tract catheterization, and treatment of infections were reviewed. The paper highlighted the need for limiting urinary tract catheterization days, and the role of catheter materials and biofilms in the disease.

8.https://www.cdc.gov/infectioncontrol/guidelines/cauti/background.html
This CDC website outlines the definition, epidemiology, pathophysiology, and microbiology of catheter-associated urinary tract infections.
9.Pickard R, Lam T, MacLennan G, et al. Antimicrobial catheters for reduction of symptomatic urinary tract infection in adults requiring short-term catheterisation in hospital: a multicentre randomised controlled trial. *Lancet*. 2012 Dec 1;380(9857):1927–1935. doi: 10.1016/S0140-6736(12)61380-4.
This study evaluated the use of urinary tract catheters made of various materials in relation to catheter-associated urinary tract infections. The authors concluded that routine use of antimicrobial catheters was not supported by the trial.

Fever in the ICU

Circiumaru B , Baldock G , Cohen J. A prospective study of fever in the intensive care unit. Intensive Care Med. 1999 Jul;25(7):73–668. doi: 10.1007/s001340050928. PMID: 10470569
This study describes fever epidemiology in a general ICU located in a tertiary care inner-city institution. It concluded that fever is a common event in the ICU, and prolonged fever is associated with poor outcomes.
Ryan M , Levy MM. Clinical review: fever in intensive care unit patients. Crit Care. 2003 Jun;7(3):1–522. doi: 10.1186/cc1879. Epub 2003 Mar 8. PMID: 12793871; PMCID: PMC270667.
This review article evaluates the literature concerning the pathophysiology, treatment practices, potential benefits, and hemodynamic and metabolic costs of fever.
Obermeyer Z , Samra JK , Mullainathan S. Individual differences in normal body temperature: longitudinal big data analysis of patient records. BMJ. 2017 Dec 13;359:j5468. doi: 10.1136/bmj.j5468. PMID: 29237616; PMCID: PMC5727437.
This study evaluates individual-level body temperature and correlates it with other physiological and health measures in patients without infection. It concluded that baseline temperatures correlated with demographics, comorbid conditions, and physiology, but these factors explained only a small part of individual temperature variation and that unexplained variation in baseline temperature strongly predicted mortality.
O'Grady NP , Barie PS , Bartlett JG , et al.; American College of Critical Care Medicine; Infectious Diseases Society of America. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med. 2008 Apr;36(4):49–1330. doi: 10.1097/CCM.0b013e318169eda9. Erratum in: Crit Care Med. 2008 Jun;36(6):1992. PMID: 18379262.
This article presents clinical practice guidelines for adult patients who develop a new fever in the intensive care unit.
Laupland KB , Shahpori R , Kirkpatrick AW , Ross T , Gregson DB , Stelfox HT. Occurrence and outcome of fever in critically ill adults. Crit Care Med. 2008 May;36(5):5–1531. doi: 10.1097/CCM.0b013e318170efd3. PMID: 18434882.
This study evaluates the occurrence of fever defined by temperature > or = 38.3°C and high fever > or = 39.5°C in the critically ill and assesses its effect on ICU outcomes. It concluded that fever was not associated with increased ICU mortality, and high fever was associated with a significantly increased risk for death.
Schortgen F , Clabault K , Katsahian S , et al. Fever control using external cooling in septic shock: a randomized controlled trial. Am J Respir Crit Care Med. 2012 May 15;185(10):95–1088. doi: 10.1164/rccm.201110-1820OC. Epub 2012 Feb 23. PMID: 22366046.
This study evaluates the effect of fever control by external cooling on vasopressor requirements in patients with septic shock. It concluded that fever control using external cooling was safe and decreased vasopressor requirements and early mortality in septic shock.

MJ Kluger , W Kozak , CA Conn , LR Leon , D Soszynski . The adaptive value of fever. *Infect Dis Clin North Am*. 1996 Mar;10(1):–-20. doi: 10.1016/s0891-5520(05)70282-8. PMID: 8698984.

This article evaluates the literature concerning the survival value of fever in animal and human models. It concludes that a rise in body temperature following infection is overall beneficial and decreases morbidity and mortality.

Lee BH, Inui D, Suh GY. et al ; Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. *Crit Care*. 2012 Feb 28;16(1):R33. doi: 10.1186/cc11211. Erratum in: *Crit Care*. 2012;16(1):450. PMID: 22373120; PMCID: PMC3396278.

This study examines the association of fever and antipyretic (acetaminophen and NSAIDs) treatments with mortality in critically ill patients with and without sepsis. It concluded that in non-septic patients, high fever (≥39.5°C) was independently associated with mortality and that in septic patients, antipyretic administration was independently associated with mortality, without association of fever with mortality.

Schulman CI , Namias N , Doherty J , et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. Surg Infect (Larchmt). 2005 Winter;6(4):75–369. doi: 10.1089/sur.2005.6.369. Erratum in: *Surg Infect (Larchmt)*. 2010 Oct;11(5):495. PMID: 16433601.

This study evaluates the impact of antipyretic therapy strategies on patients admitted to the trauma intensive care unit, excluding those with traumatic brain injury. Patients were randomized into aggressive or permissive groups. The aggressive group received acetaminophen for a temperature of >38.5°C, and a cooling blanket was added for a temperature of >39.5°C. The permissive group received no treatment for a temperature of >38.5°C but instead had treatment initiated at a temperature of >40°C, at which time acetaminophen and cooling blankets were used until the temperature was <40°C. The study was stopped after the first interim analysis due to significantly higher mortality in the aggressive group.

Young P , Saxena M , Bellomo R , et al.; HEAT Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med. 2015 Dec 3;373(23):24–2215. doi: 10.1056/NEJMoa1508375. Epub 2015 Oct 5. PMID: 26436473.

This study evaluated acetaminophen use in the ICU for patients with a temperature ≥38°C who have suspected infection. The primary outcome was ICU-free days (days alive and free from the need for intensive care) from randomization to day 28. The study concluded that administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days.

Egi M , Morita K. Fever in non-neurological critically ill patients: a systematic review of observational studies. J Crit Care. 2012 Oct;27(5):33–428. doi: 10.1016/j.jcrc.2011.11.016. Epub 2012 Jan 9. PMID: 22227089.

This systematic review of observational studies assesses the association of fever with mortality in non-neurological critically ill patients. It concluded that limited evidence suggests that the recommended definition of fever (38.3°C) might be too low to predict increased mortality.

Young P , Saxena M , Eastwood GM , Bellomo R , Beasley R. Fever and fever management among intensive care patients with known or suspected infection: a multicentre prospective cohort study. Crit Care Resusc. 2011 Jun;13(2):97–102. PMID: 21627577.

This study describes the duration of fever, fever management, and outcomes among intensive care patients with fever of ≥38.0°C and known or suspected infection, excluding those with neurological injury or elective surgery. It reported the typical time course of fever in patients with known or suspected infection and concluded that these patients have more than double the mortality rate of ineligible patients.

Fulminant Colitis

Bartlett JG , Chang TW , Gurwith M , Gorbach SL , Onderdonk AB . Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med. 1978;298:531–534.

This is the first paper to correctly identify Clostridium difficile *as the pathogen responsible for pseudomembranous colitis.*

McDonald LC , Gerding DN , Johnson S , et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clinical Infect Dis. 2018;66:e1–e48.

Comprehensive guidelines for the diagnosis, management, and prevention of C. difficile *infection. Metronidazole, a long-time recommended first-line agent, was replaced in favor of vancomycin and fidaxomicin. Nucleic acid amplification testing was also recommended as a stand-alone or confirmatory test.*

Rokas KE , Johnson JW , Beardsley JR , Ohl CA , Luther VP , Williamson JC . The addition of intravenous metronidazole to oral vancomycin is associated with improved mortality in critically ill patients with *Clostridium difficile* infection. Clin Infect Dis. 2015;61:934–941.

While metronidazole is no longer recommended as a first line therapy for Clostridium difficile *infections, this study examined its use in combination with oral vancomycin for patients with fulminant colitis.*

Sailhamer EA , Carson, K , Chang Y , et al. Fulminant *Clostridium difficile* colitis. Patterns of care and predictors of mortality. Arch Surg. 2009;144(5):433–439.

Four percent of 4796 patients had fulminant C. difficile *colitis with a 35% mortality. Three independent risk factors for mortality were found.*

*Lamontagne F , Labbé A , Haeck O , et al. Impact of emergency colectomy on survival of patients with fulminant *Clostridium difficile* colitis during an epidemic caused by a hypervirulent strain. Ann Surg. 2007;245:267–272.

This is a retrospective study of 165 cases of fulminant C. difficile *colitis with 23% undergoing colectomy and 53% overall 30-day mortality. Outcomes of patients undergoing colectomy were compared to those who did not, analyzed for each of several risk factors.*

Benefit of colectomy was demonstrated for age ≥75 years, lactic acid of >2.2 and <5 mmol/L, immunocompetent patients, and a white blood cell count of >20,000/μL.

Neal MD , Alverdy JC , Hall DE , Simmons RL , Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated *Clostridium difficile* associated disease. Ann Surg. 2011;254:423–427.

This study compared 42 cases of fulminant C. difficile *infection managed by diverting ileostomy, antegrade polyethylene glycol lavage, and vancomycin flushes via ileostomy compared to historical matched controls undergoing total colectomy. Ileostomy with antegrade lavage was a safe alternative surgical option which preserved the colon.*

Truelove SC , Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. BMJ 1955;2:1041–1048.

This paper provides details of a controlled study of cortisone versus placebo in ulcerative colitis classified by disease severity in 210 patients.

Rubin DT , Ananthakrishnan AN , Siegel CA , Sauer BG , Long MD. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114: 384–413.

This provides comprehensive clinical practice guidelines on ulcerative colitis.

Lichtiger S , Present DH , Kornbluth A , et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med. 1994;330:1841–1845.

This paper describes a randomized trial showing efficacy of Cyclosporine a as rescue therapy for severe ulcerative colitis refractory to steroids.

Jarnerot G , Hertervig E , Friis–Liby I , et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study.

Gastroenterology. 2005;128:1805–1811.
This is the first randomized placebo-controlled study to show benefit of infliximab as rescue therapy in steroid-refractory ulcerative colitis patients.
Scharff JR , Longo WE , Vartanian SM , Jacobs DL , Bahadursingh AN , Kaminski DL . Ischemic colitis: spectrum of disease and outcome. Surgery. 2003;134:624–630.
Large series of patients with ischemic colitis discussing patient characteristics, clinical presentation, extent of colonic disease and outcome.
Brandt LJ , Boley SJ. Colonic ischemia. Surg Clin North Am. 1992;72:203–229.
This paper discusses the pathophysiology, clinical presentation, and management of ischemic colitis.

Necrotizing Soft Tissue Infections

Cocanour CS, Chang P, Huston JM , et al. Management and novel adjuncts of necrotizing soft tissue infections. Surg Infect (Larchmt). 2017;18(3):250–272. doi: 10.1089/sur.2016.200
An evidence-based, GRADE-recommendation review of 64 manuscripts addressing novel and adjunctive therapies in detail, including hyperbaric oxygen, IVIG, LRINEC score, antibiotics, toxic shock syndrome, and other elements.
de Prost N, Sbidian E, Chosidow O, Brun-Buisson C, Amathieu R. Management of necrotizing soft tissue infections in the intensive care unit: results of an international survey. Intensive Care Med. 2015;41:1506–1508. doi: 10.1007/s00134-015-3916-9
A letter to the editor describing an international survey the authors performed with regards to NSTI management. Their survey of NSTIs in 100 ICUs showed significant heterogeneity in most aspects of care including adherence to the latest guidelines. They identified two major and modifiable prognostic factors—delayed diagnosis of NSTI and lack of priority access to the operating room—as being of significant concern and causing delays in definitive treatment.
Fernando SM, Tran A, Cheng W , et al. Necrotizing soft tissue infection: diagnostic accuracy of physical examination, imaging, and LRINEC score. A systematic review and meta-analysis. Ann Surg. 2019;269:58–65.
Thorough, very recent review of the current state of diagnostic modalities in NSTIs, with conclusions on the utility of the various measures. Twenty-three studies were analyzed for physical examination, imaging, and Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score in diagnosis of necrotizing soft tissue infection (NSTI) in adults with a soft tissue infection clinically concerning for NSTI. Findings included: absence of any single feature of the physical examination feature was found to be insufficient to rule-out NSTI, CT is superior to plain radiography, and LRINEC had poor sensitivity, ruling it out as a test to exclude the diagnosis of NSTI. The authors felt that given the poor sensitivity of these diagnostic modalities, high clinical suspicion and early surgical consultation remain the most important factors in early diagnosis.
Jeffrey S, Ustin JS, Malangoni MA. Necrotizing soft-tissue infections. Crit Care Med. 2011;39:2156–2162.
In this clear, succinct paper by Drs. Ustin and Malangoni, all the key elements of NSTIs are covered with a solid evidence-based approach to the literature, and with explicit recommendations regarding diagnosis, critical care, antimicrobials, source control, and adjunctive treatments. An excellent first-line reference to utilize when treating these diseases. The sometimes confusing issue of microbiologic classification is clear and reflects the latest understanding and impact of individual microorganisms.
Lauerman MH, Scalea TM, Eglseder WA, Pensy R, Stein DM, Henry S. Physiology, not modern operative approach, predicts mortality in extremity necrotizing soft tissue infections at a high-volume center. Surgery. 2018;164:105–109.
This review looks at mortality in patients with NSTIs at a large referral center with aggressive attempts to preserve limbs. Their results suggest that the aggressive limb salvage approach as opposed to early amputation did not adversely affect mortality at their center, and that patient outcome with regards to mortality was instead related to the physiology of the patient

and their response.

Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med. 2018;44:925 – 928.

Central to any discussion of the intensive care of critically ill patients suffering from sepsis are the Surviving Sepsis guidelines. The two references above are the 2016 Surviving Sepsis guidelines, and a 2018 update urging that previous 3- and 6-hour bundles be moved to a more aggressive timeline of a 1-hour bundle, including measurement of lactate, blood cultures, broad spectrum antibiotics, crystalloid infusion, and vasopressors to restore blood pressure and perfusion.

Parks T, Wilson C, Curtis N, Norrby-Teglund A, Sriskandan S. Polyspecific intravenous immunoglobulin in clindamycin-treated patients with streptococcal toxic shock syndrome: a systematic review and meta-analysis. Clin Infect Dis. 2018;67:1434–1436.

The authors performed a small meta-analysis of five studies to evaluate the effect of intravenous immunoglobulin (IVIG) on mortality in clindamycin-treated NSTIs with streptococcal toxic shock syndrome. Mortality fell from 33.7% to 15.7% in the pooled data with a p value of 0.01. While encouraging, the results certainly should be viewed with caution; only one of the five studies was randomized and none of the studies achieved a significantly decreased mortality on their own, and clindamycin is not the antimicrobial of choice in Group a streptococcal NSTIs.

Peetermans M, de Prost N, Eckmann C, Norrby-Teglund A, Skrede S, De Waele JJ. Necrotizing skin and soft-tissue infections in the intensive care unit. Clin Microbiol Infect. 2020;26:8.

A meta-analysis of NSTIs using PubMed and Cochrane. From an initial search result of 435 papers, it was narrowed down to 222 manuscripts. Some additional granularity was deduced by analysis of the data; overall, a good summary of a large amount of recent clinical data.

Rhodes A, Evans LE, Alhazzani W , et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock. Intensive Care Med. 2017 Mar;43(3):304–377. doi: 10.1007/s00134-017-4683-6. Epub 2017 Jan 18.

Stevens DL, Bisno AL, Chambers HF , et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10–52.

A panel of national experts was convened by the Infectious Diseases Society of America (IDSA) to update the 2005 guidelines for the treatment of skin and soft tissue infections (SSTIs). This is an antimicrobial-centered review which covers the gamut of skin and soft tissue infections, and is an evidence-based, expert consensus guideline that could reasonably be considered to be the most definitive guide on the most appropriate antibiotics for these infections. It covers other elements of treatment as well and is an excellent overall resource.

Bulger EM, Maier RV, Sperry J, et al. A novel drug for treatment of necrotizing soft-tissue infections. JAMA Surg. 2014 Jun 1;149(6):528–529.

Bulger EM, May A, Dankner W, Maislin G, Robinson B, Shirvan A. Validation of a clinical trial composite endpoint for patients with necrotizing soft tissue infections. J Trauma Acute Care Surg. 2017 May 22;83(4):622–627.

Bulger EM, May AK, Robinson BRH, et al. A novel immune modulator for patients with necrotizing soft tissue infections (NSTI): results of a multicenter, phase 3 randomized controlled trial of Reltecimod (AB 103). Ann Surg. 2020 Jul 8;272(3):469–478.

Sepsis I: Antibiotic Therapy

Paoli CJ , Reynolds MA , Sinha M , et al. Epidemiology and costs of sepsis in the United States—An analysis based on timing of diagnosis and severity level. Crit Care Med. 2018; 46(12):1889–1897.

This was a retrospective observational study. There were 2,566,689 adult patients with sepsis. The overall mortality was 12.5%, but it increased with increasing disease severity (5.6% for sepsis without organ dysfunction, 14.9% for severe sepsis, and 34.2% for septic

shock). Similarly, the hospital cost of the admission increased with increasing disease severity. Sepsis which was not diagnosed until after the admission, and more severe disease had higher economic burden and mortality.

Kumar A , Roberts D , Wood KE , et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589–1596.

This is a retrospective cohort study which evaluated 2731 patients with septic shock from 14 ICUs and 10 hospitals. The median time to effective antimicrobial therapy was 6 hours. Among patients who received antimicrobial therapy within the first hour of hypotension, there was a survival rate of 79.9%. There was an approximate decrease in survival of 7.6% with each hour that antibiotic administration was delayed. The time to initiation of antimicrobial therapy was the strongest predictor of outcome.

Herran-Monge R , Muriel-Bombin A , Garcia-Garcia MM , et al. Epidemiology and changes in mortality of sepsis after the implementation of Surviving Sepsis Campaign guidelines. J Intensive Care Med. 2019;34(9):740–750.

This was a prospective, multicenter, observational study comparing 262 patients with severe sepsis or septic shock to a historical cohort of 324 patients from 2002. The incidence of sepsis/septic shock did not change over the 10-year period, however, the implementation of the Surviving Sepsis Campaign guidelines resulted in a decrease in overall mortality. There was a lower severity of patients on ICU admission which suggests earlier diagnosis and management.

Rhodes A , Evans LE , Alhazzani W , et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304–377.

These are the most recent Surviving Sepsis Campaign guidelines which provide evidence-based recommendations on early management and resuscitation of patients with sepsis or septic shock. There were recommendation provided based on graded evidence for the screening for sepsis, initial resuscitation, diagnosis, and antimicrobial therapy.

Levy MM , Evans LE , Rhodes A . The Surviving Sepsis Campaign bundle: 2018 update. Crit Care Med. 2018;46:997–1000.

The authors review the elements of the 1-hour bundle in the treatment of sepsis.

Seymour CW , Gesten F , Prescott H , et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376:2235–2244.

There were 49,331 patients with sepsis or septic shock who were studied. Of these patients, 83% had the 3-hour sepsis bundle. The median time to completing the bundle was 1.3 hours, and the median time to administering antibiotics was 0.95 hours. The patients who received the antibiotics earlier on in their course and had the bundle completed more rapidly, had a lower risk-adjusted in-hospital mortality.

Jansen TC , van Bommel J , Schoonderbeek FJ , et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010;182:752–761.

There were 348 ICU patients with a lactate level >3 mmol/L who were randomized to receive lactate-guided resuscitation or be managed without monitoring the lactate levels (control group). Patients in the lactate group had reduced hospital mortality rates compared to the control group.

Leibovici L , Shraga I , Drucker M , et al. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med. 1998;244(5):379–386.

This was a prospective observational cohort study evaluating the in-hospital mortality rates and length of hospital stay in patients with bloodstream infections who either received appropriate empirical antibiotic therapy or inappropriate antibiotic therapy (the antibiotic regimen did not match the in vitro susceptibility of the pathogen). Of 3440 patients with bloodstream infections, 2158 received appropriate antibiotic therapy. The inappropriate antibiotic therapy group was associated with higher mortality rates.

Micek ST , Welch EC , Khan J , et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. Antimicrob Agents Chemother. 2010;54(5):1742–1748.

Seven-hundred-sixty ICU patients with severe sepsis or septic shock from gram-negative bacteremia were evaluated. Patients who received antibiotic regiments directed against gram-negative bacteria were less likely to receive inappropriate initial antimicrobial therapy compared to patients receiving antibiotic monotherapy.

Paul M , Lador A , Grozinsky-Glasberg S , et al. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst Rev. 2014.

This was a systematic review of randomized controlled trials that compared patients with sepsis who received beta lactam monotherapy as their initial antibiotic therapy to those who received both beta lactam and an aminoglycoside. There were 69 studies with 7863 patients included in the analysis. There was no decrease in mortality and an increased risk of nephrotoxicity in the beta lactam and aminoglycoside group compared to the monotherapy group.

Jimenez MF , Marshall JC . Source control in the management of sepsis. Intensive Care Med. 2001;27:S49–S62.

There were evidence-based recommendations based on graded evidence provided on source control in the management of sepsis. There are recommendations provided as answers to common questions for source control management of sepsis.

Azuhata T , Kinoshita K , Kawano D , et al. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care. 2014;18(3):R87.

This was a prospective observational study evaluating 154 patients with GI perforation with septic shock. The time from admission to initiation of surgery for source control that was associated with more favorable outcomes was within 6 hours of admission.

Sepsis II: Monitoring and Resuscitation

Funk DJ , Parrillo JE , Kumar A . Sepsis and septic shock: a history. Crit Care Clin. 2009; 125(1):83–101.

The authors provide a historical perspective of the name and understanding of sepsis.

Beal AL , Cerra FB . Multiple organ failure syndrome in the 1990s: systemic inflammatory response and organ dysfunction. JAMA. 1994;271(3):226–233.

The authors review the pathophysiology of SIRS and MODS, and emphasize definitions, common clinical patterns, metabolic responses, and pathophysiological changes. A brief discussion of treatment concepts is also included.

Bone RC , Balk RA , Cerra FB , et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: the ACCP/SCCM consensus conference committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644–1655.

The first consensus definition of sepsis with collaboration from the American College of Critical Care Medicine and the Society of Critical Care Medicine.

Vincent JL , Moreno R , Takala J , et al. Working group on sepsis-related problems of the European Society of Intensive Care Medicine: the SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22(7):707–710.

The authors provide a validated use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. This was a working group on “sepsis- related problems” of the European Society of Intensive Care Medicine.

Singer M , Deutschman CS , Seymour CW , et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–810.

The third and latest iteration of the definition based on further understanding of the disease pathogenesis and etiology.

Nguyen HB , Jaehne AK , Jayaprakash N , et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. Crit Care.

2016;20(1):160.
The authors compare three large RCTs comparing EGDT and standard care and found no significant difference between them. While reporting an all-time low sepsis mortality, the authors question the continued need for all of the elements of early goal-directed therapy or the need for protocolized care for patients with severe and septic shock.
Rhodes A , Evans LE , Alhazzani W , et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017 Mar;43(3):304–377. doi: 10.1007/s00134-017-4683-6. Epub 2017 Jan 18.
The authors present the international consensus guidelines for management of sepsis and the recent inclusion of the new sepsis definition. Here the 3- and 6-hour bundles are combined into the 1-hour bundle.
Levy MM , Evans LE , Rhodes A . The Surviving Sepsis Campaign bundle: 2018 update. Intensive Care Med. 2018 Jun;44(6):925–928. doi: 10.1007/s00134-018-5085-0. Epub 2018 Apr 19.
Here the 3- and 6-hour sepsis bundles are combined into the 1-hour bundle.
Rivers E , Nguyen B , Havstad S , et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–1377.
Rivers E , Nguyen B , Havstad S , et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–1377.
Nguyen HB , Jaehne AK , Jayaprakash N , et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. Crit Care. 2016;20(1):6–11.
Levy MM , Gesten FC , Phillips GS , et al. Mortality changes associated with mandated public reporting for sepsis: the results of the New York State initiative. Am J Respir Crit Care Med. 2018;198(11):1406–1412.

Steroids in Septic Shock

Annane D . The role of ACTH and corticosteroids for sepsis and septic shock: an update. Front Endocrinol. 2016;7.
Review of rationale behind mechanism of disrupted HPA axis, corticosteroids effect on cardiovascular and organ function, and potential complications.
Schumer W . Steroids in the treatment of clinical septic shock. Ann Surg. 1979;184(3):3–933.
Early double-blinded, placebo-controlled, three-arm trial over a 9 year period (1967–1976) of short-course high-dose 30 mg/kg methylprednisolone, 6 mg/kg dexamethasone, and placebo, which demonstrated a 25–30% improvement in mortality among 172 septic VA patients and a subsequent retrospective review of 328 patients.
Sprung CL , Caralis PV , Marcial EH , et al. The effects of high-dose corticosteroids in patients with septic shock. N Engl J Med. 1984;311(18):43–1137.
Double-blinded, placebo-controlled, three-arm trial at Miami hospitals in 1979–1982 found that methylprednisolone and dexamethasone improved shock reversal at 24 hours and mortality at 133 hours but subsequently disappeared around 200 hours. Dexamethasone significantly increased rate of superinfections.
Bone RC , Fisher CJ , Clemmer TP , Slotman GJ , Metz CA , Balk RA . A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med. 1987;317(11):3–865.
Double-blinded, placebo-controlled, multi-center randomized trial in the US from 1982–1985, found that high-dose methylprednisolone did not improve shock prevention, shock reversal, and overall mortality. Steroids increased mortality in subgroup of kidney failure and increased mortality related to secondary infections.
Annane D , Sébille V , Charpentier C , et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288(7):71–862.

A multi-center, double-blinded, parallel group randomized trial in France found that hydrocortisone and fludrocortisone prolonged the median time to death in participants with relative adrenal insufficiency, and hypotension despite fluids and vasopressors, within 8 hours of septic shock onset. This trial was powered in a 1-sided test to detect a 20% reduction in mortality with corticosteroids in non-responders, assuming a baseline mortality rate of 95% in the placebo group. Steroids prolonged primary outcome of median time to death from 12 to 24 days (HR 0.67, 95%CI 0.47–0.95, p = 0.02) and reduced median time to vasopressor withdrawal in non-responders (7 vs. 10 days, HR 1.91, 95%CI 1.29–2.84, p = 0.001) and all patients (7 vs. 9 days, HR 1.54, 95%CI 1.10–2.16, p = 0.01).

Sprung CL , Annane D , Keh D , et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):24–111.

The Corticosteroid Therapy for Septic Shock (CORTICUS) trial was an international, double-blinded, randomized, placebo-controlled study that found hydrocortisone 50 mg every 6 hours for 5 days tapered to day 12 in septic shock requiring vasopressors did not have an effect on 28-day mortality (non-responders 39.2% vs. 36.1%, p = 0.69), but was likely underpowered. The median time until shock reversal was shorter in the hydrocortisone group for all patients (3.3 vs. 5.8 days, p <0.001). Separate outcomes of new sepsis or septic shock were combined post-hoc and found to be increased in the intervention group (OR 1.37, 95%CI 1.05–1.79).

Annane D , Renault A , Brun-Buisson C , et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med. 2018;378(9):18–809.

The Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial was a multi-center, double-blinded, randomized, placebo-controlled study that found steroids reduced 90-day mortality (43.0% vs. 49.1%, RR 0.88, 95%CI 0.78-0.99, p = 0.03), but fragility index of 3. It was initially designed to evaluate hydrocortisone plus fludrocortisone and drotrecogin alfa in a 2-by-2 factorial design, but continued with two parallel groups when drotrecogin alfa was withdrawn.

Venkatesh B , Finfer S , Cohen J , et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med. 2018;378(9):797–808.

The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial was an international, double-blinded, randomized, placebo-controlled, parallel-group study with enough patients to provide 90% power to detect a 5% absolute risk reduction, from a baseline mortality rate of 33%. The intervention was hydrocortisone infusion 200 mg per day for 7 days without fludrocortisone. Time to randomization was 21 hours on average (19.1% <6 hours, 27.4% 6–12 hours, 23.6% 12–18 hours, 29.9% >18 hours). There were no differences in 90-day (27.9% vs. 28.8%, p = 0.50), or 28-day mortality but steroids improved median days to shock resolution (3 vs. 4 days, HR 1.32; 95%CI 1.23–1.41, P ≤0.001), time to cessation of initial ventilation (6 vs. 7 days, HR 1.13; 95%CI 1.05–1.22, P ≤0.001), time to discharge from ICU (10 vs. 12 days, HR 1.14, 95%CI 1.06–1.23, P ≤0.001) and number of transfusions (37.0% vs. 41.7%, OR 0.82; 95%CI 0.72–0.94, P = 0.004). Four of six serious adverse events were in steroid group (two myopathy, one ischemic bowel and one circulatory shock). Long-term neuromuscular weakness was not assessed. Interestingly, only Australia out of all other regions had an improvement in 28-day mortality (19.9% vs. 23.3%, OR 0.82, 95%CI 0.68–0.98) and trended towards improvement in 90-day mortality with steroids.

Annane D , Bellissant E , Bollaert PE , et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev*. 2019.

Cochrane review updated in 2019 and summarized the effects of 61 trials in sepsis involving 12,192 total participants and concluded that corticosteroids probably slightly reduce 28-day mortality (RR 0.91, 95%CI 0.84–0.99, p = 0.04; 11,233 participants; 50 studies; moderate certainty), reduced ICU and hospital length of stay, with a mean difference of about 1 day and 1.5 days, and increased the number of participants with shock reversal at day 7. The subgroup of CIRCI did not have an improvement in mortality with corticosteroids (RR 0.92, 95%CI 0.82–1.03, p = 0.16; 1079 participants; 12 studies; I2 = 0%). There was an increased the risk of muscle weakness, hypernatremia, and hyperglycemia.

Fang F , Zhang Y , Tang J , et al. Association of corticosteroid treatment with outcomes in adult patients with sepsis. JAMA Intern Med. 2019;179(2):213.

Recent systematic review and meta-analysis of corticosteroid therapy in patients with sepsis is associated with reduction in 28-day mortality (RR 0.90, 95%CI 0.82–0.98; I2 = 27%), ICU and in-hospital mortality, ICU length of stay, SOFA at day 7 and time to resolution of shock.

Rochwerg B , Oczkowski SJ , Siemieniuk RAC , et al. Corticosteroids in sepsis. Crit Care Med. 2018;46(9):20–1411.

Recent systematic review and meta-analysis found that corticosteroids may achieve a small reduction or no reduction in short-term mortality (RR 0.93, 95%CI 0.84–1.03; 1.8% absolute risk reduction), small effect on long-term mortality (RR 0.94, 95%CI 0.89–1.00; 2.2% absolute risk reduction), small reductions in length of stay in ICU and hospital, higher rates of shock reversal at day 7, lower SOFA scores at day 7, and higher risk of hypernatremia, hyperglycemia, and neuromuscular weakness.

Venkatesh B , Finfer S , Cohen J , et al. Hydrocortisone compared with placebo in patients with septic shock satisfying the sepsis-3 diagnostic criteria and APROCCHSS study inclusion criteria. Anesthesiology. 2019;131(6):300–1292.

In a post-hoc analysis of ADRENAL participants who fulfilled either sepsis-3 definition or APROCCHSS inclusion criteria, overall mortality rates at 90 days were higher, but there was no effect of hydrocortisone regardless of analysis with either odds ratio or rate ratio.

Venkatesh B , Cohen J . The utility of the corticotropin test to diagnose adrenal insufficiency in critical illness: an update. Clin Endocrinol. 2015;83(3):97–289.

Review of evidence concluding that the use of corticotropin test in assessing adrenocortical function and guiding steroid therapy in critically ill patients is limited due to several confounding variables, methodology differences, and lack of relationship between the test and severity of illness.

Treatment of Abdominal Sepsis

Mazuski JE , Tessier JM , May AK , et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. Surg Infect (Larchmt). 2017;18(1):6–17.

The most recent revision of the Surgical Infection Society's Guidelines on the management of intraabdominal infections. Reviews and provides a reference for the diagnosis, treatment, and management including critically ill patients with abdominal sepsis and risk factors for mortality and failure of source control.

Kumar A , Roberts D , Wood KE , et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):96–1589.

A retrospective cohort study performed in 14 ICUs in Canada and the United States of 2731 patients with septic shock. Includes a significant portion of patients with abdominal sepsis and demonstrates a pronounced association of time to initiation of antimicrobial therapy with survival.

Kumar A , Ellis P , Arabi Y , et al. Initiation of inappropriate antimicrobial therapy results in a five-fold reduction of survival in human septic shock. Chest. 2009;136(5):48–1237.

A 10 year retrospective analysis of 5715 patients with septic shock admitted to 22 medical centers in Canada, the United States, and Saudi Arabia, examining the impact of inappropriate empiric antimicrobial therapy on outcome. Includes a large cohort of abdominal sepsis patients and demonstrates a very strong association of inappropriate therapy with survival.

Anaya DA , Nathens AB . Risk factors for severe sepsis in secondary peritonitis. Surg Infect (Larchmt). 2003;4(4):62–355.

A retrospective analysis of 11,202 patients with peritonitis from a statewide dataset to determine the incidence of and risk factors for severe sepsis in abdominal sepsis. Multivariate analysis was performed to estimate the impact of sepsis on outcome.

Barie PS , Vogel SB , Dellinger EP , et al. A randomized, double-blind clinical trial comparing cefepime plus metronidazole with imipenem-cilastatin in the treatment of complicated intra-abdominal infections. Cefepime Intra-abdominal Infection Study Group. Arch Surg. 1997;132(12):302–1294.

In an analysis of a randomized, double-blind trial examining 2 antibiotic regimens including 350 patients from 17 centers in the US and Canada, APACHE II and prolonged pre-study length of hospitalization as the only two independent risk factors for treatment failure. Demonstrates the high rate of failure of source control when patients have high APACHE II scores.

Koperna T , Schulz F . Relaparotomy in peritonitis: prognosis and treatment of patients with persisting intraabdominal infection. World J Surg. 2000;24(1):2–73.

Retrospective case-control study including 105 patients who required relaparotomy for failed source control. The authors identify risk factors for failure of source control and that delay in relaparotomy beyond 48 hours in patients with failed source control was associated with increased mortality.

Crabtree TD , Pelletier SJ , Antevil JL , Gleason TG , Pruett TL , Sawyer RG . Cohort study of fever and leukocytosis as diagnostic and prognostic indicators in infected surgical patients. World J Surg. 2001;25(6):44–739.

Prospective, 1-year, single center observational study of all surgical patients suspected of having an infectious complication to examine the incidence of fever and leukocytosis and their diagnostic and prognostic value.

Sawyer RG , Claridge JA , Nathens AB , et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372(21):1996–2005.

Landmark Surgical Infection Society sponsored randomized trial examining two different periods of antibiotic therapy following source control in complicated intra-abdominal infections; a fixed duration of antibiotic therapy (4+/- 1 calendar days) versus duration 2 days beyond resolution of fever, leukocytosis, and ileus for a maximum of 10 days.

Diabetic Ketoacidosis

Kitabchi AE , Umpierrez GE , Miles JM , Fisher JN . Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335–1343. doi:10.2337/dc09-9032

Consensus statement from the ADA describing features and treatment of DKA and hyperosmolar hyperglycemic state (HHS).

Benoit SR , Zhang Y , Geiss LS , Gregg EW , Albright A . Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality—United States, 2000–2014. MMWR Morb Mortal Wkly Rep. 2018;67(12):362–365. doi:10.15585/mmwr.mm6712a3

Data analysis from the CDC US Diabetes Surveillance System showing rising rates of DKA hospitalizations, particularly in younger people with postulated causes.

Chua HR , Venkatesh B , Stachowski E , et al. Plasma-Lyte 148 vs. 0.9% saline for fluid resuscitation in diabetic ketoacidosis. J Crit Care. 2012;27(2):138–145. doi:10.1016/j.jcrc.2012.01.007

Small, retrospective study comparing laboratory and clinical outcomes of Plasma-Lyte versus normal saline in DKA. Patients receiving Plasma-Lyte had faster resolution of acidemia in first 12 hours and less hyperchloremia.

Mahler SA , Conrad SA , Wang H , Arnold TC . Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. Am J Emerg Med. 2011;29(6):670–674. doi:10.1016/j.ajem.2010.02.004

Small, prospective, randomized study of Plasma-Lyte versus normal saline resuscitation in DKA via monitoring of serum chloride, bicarbonate, and calculated anion gap. The study achieved statistical significance showing Plasma-Lyte as opposed to normal saline prevented hyperchloremic metabolic acidosis.

van Zyl DG , Rheeder P , Delport E . Fluid management in diabetic-acidosis Ringer's lactate versus normal saline: a randomized controlled trial. QJM. 2012;105(4):337–343. doi:10.1093/qjmed/hcr226

Small, randomized trial of normal saline versus Lactated Ringer's in DKA showing nonsignificant trends toward faster resolution of acidemia; results may have been affected by premature study cessation due to inability to obtain intended sample size.

Kitabchi AE , Murphy MB , Spencer J , Matteri R , Karas J . Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care. 2008;31(11):2081–2085. doi:10.2337/dc08-0509

Small, randomized trial of insulin regimens in DKA, one with a bolus and two without, showing no difference in time to DKA resolution with bolus.

Goyal N , Miller JB , Sankey SS , Mossallam U . Utility of initial bolus insulin in the treatment of diabetic ketoacidosis. J Emerg Med. 2010;38(4):422–427. doi:10.1016/j.jemermed.2007.11.033

Prospective, observational chart review of 150 DKA presentations which showed no clinically relevant superiority to an insulin bolus plus infusion regimen compared to infusion without bolus; there was a trend toward higher incidence of hypoglycemia in the bolus group.

Umpierrez G , Korytkowski M . Diabetic emergencies-ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol. 2016;12(4):222–232. doi:10.1038/nrendo.2016.15

Thorough and well-referenced review of the epidemiology, pathophysiology, and management of DKA and HHS, including risk of DKA from SGLT2 inhibitors. Excellent graphics, including management flowcharts and highlighted treatment protocols. Detailed discussion of presentation and management of hypoglycemia is also helpful to the intensivist.

Long B , Willis GC , Lentz S , Koyfman A , Gottlieb M . Evaluation and management of the critically ill adult with diabetic ketoacidosis. J Emerg Med. 2020;59(3):371–383. doi:10.1016/j.jemermed.2020.06.059

Best review of DKA from a critical care perspective; references ADA definitions and guidelines, discusses controversies in management. Offers clinically useful, practical recommendations with a comprehensive list of references.

Kamel KS , Halperin ML . Acid–base problems in diabetic ketoacidosis. N Engl J Med. 2015;372(6):546–554. doi:10.1056/nejmra1207788

A review of the biochemical basis of DKA, emphasizing chemical formulae. Good discussion of the pathophysiology of cerebral edema and controversies of its management.

Umpierrez GE , Jones S , Smiley D , et al. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. Diabetes Care. 2009;32(7):1164–1169. doi:10.2337/dc09-0169

Small, randomized controlled trial important for showing that in DKA, treatment transition from IV infusion insulin to NPH insulin resulted in a higher incidence of hypoglycemia as compared to transition to glargine or glulisine insulin.

Glaser, N . Diabetic ketoacidosis in children: cerebral injury (cerebral edema) In: Wolfsdorf J , Randolph A , eds. UpToDate. Waltham, MA: *UpToDate* ; 2020.https://www.uptodate.com/contents/diabetic-ketoacidosis-in-children-cerebral-injury-cerebral-edema; last updated November 12, 2020

The author, a lead researcher in studying pediatric neurologic injury associated with DKA, provides a comprehensive review of the most recent studies and hypotheses about the pathophysiology and causative factors of cerebral edema in children with DKA.

Glucose Management in the ICU

Van den Berghe G , Wouters P , Weekers F , et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–1367.

Landmark RCT including adult critically ill patients admitted to the surgical ICU (n =1548). The RCT showed a reduction in morbidity and mortality by tight glucose control, provided with a standardized protocol (arterial blood glucose measurements by blood gas analyzer, avoidance of insulin boluses). According to feeding guidelines at that time, all patients received early parenteral nutrition. This feeding practice was subsequently shown to be detrimental, also when feeding-induced hyperglycemia is treated.

Van den Berghe G , Wilmer A , Hermans G , et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–461.

First RCT in adult critically ill patients admitted the medical ICU (n = 1200). The RCT confirmed a beneficial impact of tight glucose control, provided with a standardized protocol (predominantly arterial blood glucose measurements by blood gas analyzer, avoidance of insulin boluses). According to feeding guidelines at that time, all patients received early parenteral nutrition. This feeding practice was subsequently shown to be detrimental, also when feeding-induced hyperglycemia is treated.

Vlasselaers D , Milants I , Desmet L , et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009;373(9663):547–556.

This pioneer RCT in critically ill children (n = 700) demonstrated that tight glucose control significantly decreased morbidity and mortality as compared to tolerating stress hyperglycemia, while increasing the risk of hypoglycemia. In the intervention group, continuous intravenous insulin was titrated to maintain blood glucose within the normal age-adjusted fasting range for blood glucose (50–80 mg/dL for infants, 70–100 mg/dL for children older than 1 year). The glucose control protocol was well standardized. All patients received early parenteral nutrition.

Mesotten D , Gielen M , Sterken C , et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. JAMA. 2012;308(16):1641–1650.

Prospective follow-up study of critically ill children randomized to tight versus liberal glucose control, including 569 (84%) patients enrolled in the parent RCT (Vlasselaers et al. Lancet 2009). The study showed that clinical benefit was maintained on the long-term. Indeed, full neurodevelopmental testing 4 years after randomization revealed that children randomized to tight glucose control behaved similar or better on selected neurocognitive tasks. A short episode of hypoglycemia was not associated with long-term neurocognitive harm.

Gunst J , De Bruyn A , Van den Berghe G . Glucose control in the ICU. Curr Opin Anaesthesiol. 2019;32(2):156–162.

Recent review summarizing the clinical evidence on tight glucose control, as well as the open questions and recent areas of improvement (software-guided glucose control, continuous glucose monitoring, closed-loop blood glucose control).

Ellger B , Debaveye Y , Vanhorebeek I , et al. Survival benefits of intensive insulin therapy in critical illness: impact of maintaining normoglycemia versus glycemia-independent actions of insulin. Diabetes. 2006;55(4):1096–1105.

Detailed animal study elucidating the impact of glucose lowering versus increasing insulin availability on outcome of critically ill animals. The study showed that maintenance of normoglycemia rather than high insulin levels improved morbidity and mortality.

Gunst J , Van den Berghe G . Blood glucose control in the ICU: don't throw out the baby with the bathwater! Intensive Care Med. 2016;42(9):1478–1481.

Recent opinion article as part of series of opinion papers on tight glucose control in the ICU. Apart from providing a brief overview of clinical evidence, the article summarizes animal evidence and mechanistic studies on how preventing hyperglycemia with insulin therapy may be beneficial.

NICE-SUGAR Study Investigators ; Finfer S , Chittock DR , Su SY , et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–1297.

The largest multicenter RCT on tight versus liberal blood glucose control in adult critically ill patients (n = 6104). The RCT reported increased mortality by tight glucose control, fueling a vivid debate on the topic. The RCT has been criticized for the use of potentially inaccurate metrics to perform tight glucose control.

NICE-SUGAR Study Investigators ; Finfer S , Liu B , Chittock DR , et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–1118.

This secondary analysis of the NICE-SUGAR RCT attributed the clinical harm of tight glucose control to the increased incidence of severe hypoglycemia.

Van den Berghe G , Wilmer A , Milants I , et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes. 2006;55(11):3151–3159.

This secondary analysis of the adult Leuven RCTs on tight versus liberal glucose control (n = 2748) addressed important questions raised by the first adult RCTs. The study showed that tight glucose control decreased mortality in all subgroups of critically ill patients, except in

patients with pre-admission diabetes mellitus. Also, benefit was present regardless of the parenteral glucose load. Thirdly, the study could not attribute short-term harm to a brief episode of iatrogenic hypoglycemia. Finally, the study suggested a dose-response relationship between blood glucose lowering and outcome. Indeed, patients with intermediate blood glucose control (110–150 mg/dL) had better survival than patients with blood glucose above 150 mg/dL, but worse outcome as compared to patients with blood glucose between 80 and 110 mg/dL.

Van den Berghe G , Wouters P , Weekers F , et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–1367.

Van den Berghe G , Wilmer A , Hermans G , et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–461.

Vlasselaers D , Milants I , Desmet L , et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009;373(9663):547–556.

NICE-SUGAR Study Investigators ; Finfer S , Chittock DR , Su SY , et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–1297.

Gunst J , De Bruyn A , Van den Berghe G . Glucose control in the ICU. Curr Opin Anaesthesiol. 2019;32(2):156–162.

Acute Stroke

Broderick JP , Palesch YY , Demchuk AM , et al. Endovascular therapy after intravenous tPA versus tPA alone for stroke. *N Engl J Med*. 2013;68:893–903.

In this randomized controlled trial (RCT) in 656 patients with AIS who received IV rt-PA within 3 hours of stroke onset, additional EVT did not result in improved functional outcomes.

Ciccone A , Valvassori L , Nichelatti M , et al. Endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2013;368:904–913.

In this RCT in 362 patients with AIS who were randomized to IV rt-PA or EVT within 4.5 hours of stroke onset, EVT was not superior to treatment with IV rt-PA.

Kidwell CS , Jahan R , Gornbein J , et al. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368:914–923.

In this trial, 118 patients with AIS due to LVO were randomized within 8 hours of stroke onset to EVT vs. standard care. EVT was not superior to standard care.

Berkhemer OA , Fransen PSS , Beumer D , et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20.

In this trial, 500 patients with AIS due to LVO were randomized within 6 hours of stroke onset to either EVT plus standard care or standard care alone. EVT improved functional outcomes at 90 days and was safe.

Campbell BCV , Mitchell PJ , Kleinig TJ , et al. Endovascular therapy for ischemic stroke with perfusion imaging selection. *N Engl J Med*. 2015;372:1009–1018.

In this trial, 70 AIS patients with LVO and evidence of salvageable brain tissue and ischemic core <70 mL on perfusion CT were randomized within 4.5 hours of stroke onset to either EVT or IV rt-PA. EVT, compared with alteplase alone, improved reperfusion, early neurologic recovery at day 3, and functional outcome at 90 days.

Goyal M , Demchuk AM , Menon BK , et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030.

In this trial, 316 patients with AIS due to LVO who had a small infarct and good collateral circulation were randomized within 12 hours of stroke onset to either EVT plus standard care or standard care alone. EVT improved functional outcomes at 90 days and reduced mortality.

Jovin TG , Chamorro A , Cobo E , et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306.

In this trial, 206 patients with AIS due to LVO were randomized within 8 hours of stroke onset to either medical therapy including IV rt-PA or medical therapy including IV rt-PA and EVT. EVT increased the rate of functional independence at 90 days.

Saver JL , Goyal M , Bonafe A , et al. Stent retriever thrombectomy after intravenous tPA vs. tPA alone in stroke. *N Engl J Med*. 2015;372:2285–2295.
In this RCT trial, 196 patients with AIS due to LVO were randomized to within 6 hours of stroke onset to IV rt-PA alone or IV rt-PA and EVT. EVT improved functional outcomes at 90 days.
Nogueira RG , Jadhav AP , Haussen DC , et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21.
Albers GW , Marks MP , Kemp S , et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718.
In this RCT trial, 182 AIS patients with LVO, initial infarct volume <70 mL and a ratio of the volume of ischemic tissue on perfusion MRI or CT to infarct volume of 1.8 or more were randomized within 6–16 hours of stroke onset to EVT plus medical therapy vs. medical therapy alone. EVT resulted in better functional outcomes at 90 days.

Subarachnoid Hemorrhage

Wiebers DO , Whisnant JP , Huston J, 3rd , et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* . 2003;362:103–110.
This was a landmark multicenter prospective study that aimed to assess the natural history of unruptured aneurysms and determine the risk associated with treatment versus observation.
Milinis K , Thapar A , O'Neill K , Davies AH . History of aneurysmal spontaneous subarachnoid hemorrhage. *Stroke* . 2017;48:e280–e283.
This is a thorough overview of the history of aneurysmal subarachnoid hemorrhage. It provides an excellent historical perspective on the development of our understanding intracranial aneurysms and the advances in our treatment of them.
Lawton MT , Vates GE . Subarachnoid hemorrhage. *N Engl J Med*. 2017;377:257–266 .
A thorough overview of aneurysmal subarachnoid hemorrhage including a comprehensive literature review and description of epidemiology, clinical presentation, treatment, and current controversies.
Molyneux A , Kerr R , Stratton I , et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* . 2002;360:1267–1274.
This is a randomized, multicenter trial comparing clipping and endovascular treatment in 2143 patients presenting with ruptured intracranial aneurysms. In patients where both treatments were suitable, a survival benefit was found in those treated with endovascular coiling compared to surgical clipping.
Connolly ES, Jr. , Rabinstein AA , Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* . 2012;43:1711–1737.
This is a literature review that summarizes the literature and guidelines on the epidemiology, clinical presentation, and management of aneurysmal subarachnoid hemorrhage.
Perry JJ , Stiell IG , Sivilotti ML , et al. Clinical decision rules to rule out subarachnoid hemorrhage for acute headache. *JAMA* . 2013;310:1248–1255.
This is large prospective multicenter study evaluating clinical risk factors that predict the presence of subarachnoid hemorrhage in patients presenting with headache.
Hunt WE , Hess RM . Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg*. 1968;28:14–20.
This is a landmark paper that summarizes the risk of mortality of aneurysmal subarachnoid hemorrhage patients based on clinical presentation on admission. The results of this study formed the basis for the widely used Hunt–Hess grading scale in describing the severity of clinical presentation.
Hijdra A , van Gijn J , Nagelkerke NJ , Vermeulen M , van Crevel H . Prediction of delayed cerebral ischemia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage.

Stroke. 1988;19:1250–1256.
This study analyzes variables associated with delayed cerebral ischemia, rebleeding, and poor outcomes in patients with aneurysmal subarachnoid hemorrhage. The authors found that death or severe disability after 3 months was best predicted by amount of subarachnoid hemorrhage and grade on the Glasgow Coma Scale. The results of this study provides the basis for the World Federation of Neurological Surgeons (WFNS) grading scale.
Hillman J , Fridriksson S , Nilsson O , Yu Z , Saveland H , Jakobsson KE . Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg*. 2002;97:771–778.
This prospective study found that an early and short course of antifibrinolytics reduced the risk of early rebleeding in subarachnoid hemorrhage. This provides a medical alternative in cases where early treatment of ruptured aneurysms cannot be achieved.
McDougall CG , Spetzler RF , Zabramski JM , et al. The Barrow Ruptured Aneurysm Trial. *J Neurosurg*. 2012;116:135–144.
This is a prospective, randomized single-center trial comparing clipping versus coil embolization in the treatment of intracranial aneurysms. There were no differences in morbidity between the surgical and endovascular group, but rates of retreatment and complete obliteration favored patients who underwent clipping compared to coiling.
Spetzler RF , McDougall CG , Zabramski JM , et al. Ten-year analysis of saccular aneurysms in the Barrow Ruptured Aneurysm Trial. *J Neurosurg*. 2019;132:771–776.
This study presents the 10-year results of the Barrow Ruptured Aneurysm Trial (BRAT) comparing clipping and endovascular coiling of ruptured aneurysms. There was no statistically significant difference in clinical outcomes between the two groups.
Luther E , McCarthy DJ , Brunet MC , et al. Treatment and diagnosis of cerebral aneurysms in the post-International Subarachnoid Aneurysm Trial (ISAT) era: trends and outcomes. *J Neurointerv Surg*. 2020;12:682–687.
This paper uses an administrative database, the National Inpatient Sample, from 2004 to 2014 to describe trends in the treatment and clinical outcomes of ruptured and unruptured intracranial aneurysms. The authors confirm the increasing use of endovascular treatment for these lesions as well as the improved mortality and morbidity among both surgical and endovascular patients.

Delirium

Ely EW , Margolin R , Francis J , et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med*. 2001 Jul;29(7):79–1370.
Classic study that validated the CAM-ICU instrument against the DSM-IV criteria for delirium. Showing it is quick, valid, and reliable for diagnosing delirium in the ICU setting.
Krewulak KD , Stelfox HT , Leigh JP , Ely EW , Fiest KM . Incidence and prevalence of delirium subtypes in an adult ICU: a systematic review and meta-analysis. *Crit Care Med*. 2018;46(12):35–2029.
Systematic review and meta-analysis including 48 studies (27,342 patients; 4550 with delirium) with showing overall pooled prevalence of 31%. These data show the majority of delirious ICU patients to have hypoactive delirium and delirium risk is higher in patients with greater severity of illness.
Saczynski JS , Marcantonio ER , Quach L , et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012 Jul 5;367(1):0–93.
Prospective study of patients 60 years of age or older undergoing coronary-artery bypass grafting or valve replacement surgery that showed that postoperative development of delirium was a risk factor for a decline in cognitive function and a prolonged period of impairment after cardiac surgery.
Deng L-X , Cao L , Zhang L-N , Peng X-B , Zhang L . Non-pharmacological interventions to reduce the incidence and duration of delirium in critically Ill patients: a systematic review and network meta-analysis. *J Crit Care*. 2020 Aug 31;60:1–824.

Recent systematic review and meta-analysis showing that multi-component strategies are overall the optimal intervention techniques for preventing delirium and reducing ICU length of stay in critically ill patients.

Inouye SK , Bogardus ST , Charpentier PA , et al. a multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999 Mar 4;340(9):76–669.

Prospective randomized controlled clinical trial in a teaching institution demonstrating that an intervention consisting of standardized protocols for the management of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration resulted in significant reductions in the number and duration of episodes of delirium in hospitalized older patients.

Pun BT , Balas MC , Barnes-Daly MA , et al. Caring for critically Ill patients with the ABCDEF bundle: results of the ICU Liberation Collaborative in over 15,000 adults. *Crit Care Med*. 2019 Jan;47(1):4–31.

Prospective, multicenter, cohort study from a national quality improvement collaborative, including patients from 68 ICUs and a total of 15,226 patients, showing that a non-pharmacological approach significantly improved survival, mechanical ventilation use, coma and delirium, restraint-free care, ICU readmissions, and post-ICU discharge disposition.

Subramaniam B , Shankar P , Shaefi S , et al. Effect of intravenous acetaminophen vs. placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: the DEXACET randomized clinical trial. *JAMA* . 2019 Feb 19;321(7):686.

First randomized controlled trial showing a significant and meaningful reduction in the incidence of delirium with the use of scheduled IV acetaminophen in patients undergoing cardiac surgery. Additionally, delirium duration, ICU length of stay, and opioid and/or opioid equivalent use in the immediate postoperative period were lower in the intervention group.

Riker RR . Dexmedetomidine vs. midazolam for sedation of critically Ill patients: a randomized trial. *JAMA* . 2009 Feb 4;301(5):489.

Multicenter, prospective, double-blind, randomized trial showing that the use of dexmedetomidine vs. midazolam achieved comparable sedation levels. Patients in the dexmedetomidine group spent less time on the ventilator, experienced less delirium, and developed less tachycardia and hypertension.

Devlin JW , Skrobik Y , Gélinas C , et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018 Sep;46(9):e825.

Most current SCCM guidelines regarding the management of delirium in the ICU.

Reade MC , Eastwood GM , Bellomo R , et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. *JAMA* . 2016 Apr 12;315(14):1460.

This study showed a potential benefit of using dexmedetomidine, in addition to standard care, for ventilated patients with agitated delirium. There was a modest reduction in time for liberation from the ventilator and a more rapid delirium resolution. It also demonstrated sedation and opioid-sparing effects.

Intractable Intracranial Hypertension

Koenig MA . Cerebral edema and elevated intracranial pressure. Continuum. 2018 Dec;24(6):1588–1602.

Comprehensive review article that describes the different types and etiologies of cerebral edema and their specific treatments; the physiological concepts of elevated intracranial pressure and its measurement and management including pentobarbital coma, hypothermia and decompressive surgery and the different herniation syndromes. Describes important distinctions between vasogenic and cytotoxic edema, diffuse and focal edema, uncal, and central posterior fossa herniation syndromes.

Stocchetti N , Maas AI . Traumatic intracranial hypertension. N Engl J Med. 2014 May 29;370(22):2121–30.

A focused review on intracranial hypertension from traumatic brain injury. Discusses pathophysiology and intracranial pressure monitoring and brief summaries of management citing evidence and offers staircase tiered management strategy.

Anika S , Fareed J , Bharath R , Nitesh V P , Gaurav G , Anil N . The historical evolution of intracranial pressure monitoring. World Neurosurg. June 2020;138: 491–7.

A comprehensive historical review of the development of intracranial pressure monitoring.

Carney N , Totten AM , O'Reilly C , et al. Guidelines for the management of severe traumatic brain injury. Neurosurgery. 2017 Jan 1;80(1):6–15.

Latest updated comprehensive guidelines for management of severe TBI. Notable updates include the inclusion of decompressive craniectomy and CSF drainage as treatments. Hyperosmolar therapy section focused on comparative effectiveness of different agents, additional nutritional recommendations, and reorganizing and renaming of chapters, including a separate CPP and BP threshold section and advanced cerebral monitoring and threshold section. Notable recommendations include SBP thresholds of 100–110 mm Hg, early feeding within 5 days. Of note, these guidelines came out before the results of the BOOST-2 trial were published.

Ropper AH . Hyperosmolar therapy for raised intracranial pressure. N Engl J Med. 2012;367:52–746.

Case based review discussing the detailed physiological mechanisms of actions of mannitol and hypertonic saline, its clinical use as well as adverse effects, evidence supporting its use, as well as addressing some controversies regarding its use.

Clifton GL , Valadka A , Zygun D , et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. Lancet Neurol. 2011;10:131–9.

Randomized, multicenter clinical trial of severe TBI patients assigned to hypothermia and cooled to 33°C for 48 hours and then gradually rewarmed or treated at normothermia, looking at the Glasgow outcome scale score at 6 months. This was a negative trial with no differences in outcomes, but it's notable that the hypothermia group had more episodes of ICP elevation than the normothermia group. The study was also stopped short for futility and was likely underpowered. It raised questions about the appropriate duration of hypothermia and complications of rewarming as well as differences in diffuse versus focal brain injury.

Roberts I , Sydenham E . Barbiturates for acute traumatic brain injury. Cochrane Database Syst Rev. 2012 Dec 12;12(12):CD000033

Cochrane review of barbiturate use for acute traumatic brain injury from seven clinical trials with a total of 341 patients. They concluded that there was no outcome or mortality benefit and that a fourth of all patient receiving barbiturates develop significant hypotension that likely offsets any benefit that may have been seen.

Hutchinson PJ , Kolias AG , Timofeev IS , et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med. 2016 Sep 22;375(12):1119–30.

Multicenter, international, randomized, parallel group, superiority clinical trial looking at decompressive craniectomy in traumatic brain injury, which was completed after the DECRA trial results were published showing a significant mortality benefit at 6 months but also higher rates of vegetative state and severe disability in the surgically treated patients. It differs substantially from DECRA in that it initiated surgical treatments as a last tier in truly refractory patients and included patients with intraparenchymal hematoma which compromised 20% of the patients. They also allowed for hemicraniectomy which DECRA excluded.

Chesnut RM , Temkin N , Carney N , et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med. 2012 Dec 27;367(26):2471–81.

The only randomized controlled trial comparing an ICP monitoring based management protocol versus a serial examination and imaging-based management protocol for severe TBI patients. Conducted in Bolivia and Ecuador because of lack of clinical equipoise and legal limitations in the US the study showed no difference in outcomes or rates of craniectomy but did result in less osmotherapy and hyperventilation and shorter duration of these treatments in the ICP monitoring group.

Okonkwo DO , Shutter LA , Moore C , et al. Brain tissue oxygen monitoring and management in severe traumatic brain injury (BOOST-II): a phase II randomized trial. Crit Care Med. 2017 Nov;45(11):14–1907.

A two-arm, single-blind, prospective randomized controlled multicenter phase II trial assessing safety and efficacy of a management protocol optimizing PbtO2 following severe TBI that showed good safety and that the addition of regional oxygen monitoring to ICP monitoring resulted in a positive trend for outcome and lower mortality.

Coagulopathy

Stephan F , et al. Thrombocytopenia in a surgical ICU. Chest. 1999;115:1363–1370.

Prospective trial investigating incidence and outcomes associated with thrombocytopenia and surgical ICU patients. The investigators found sepsis to be the major risk factor for development of thrombocytopenia and found thrombocytopenic patients had a higher ICU mortality due to increased severity of disease.

Levi M , Opal SM . Coagulation abnormalities in critically ill patients. Crit Care. 2006;10:222.

A comprehensive review detailing the diagnosis and etiology of major coagulopathies in critically ill patients. Describes multiple management strategies for treatment of coagulopathies with a focus on DIC.

Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54.

A retrospective study designed to determine the clinical importance of coagulopathy in severely injured trauma patients. The authors found that patients with acute coagulopathy had a significantly higher mortality rate, and the incidence of coagulopathy increased with the severity of the injury.

Vanderschueren S , et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med. 2000;28:1871–1876.

A prospective observational cohort study aimed to identify the incidence and prognosis of thrombocytopenia in the ICU. Found thrombocytopenia to be risk marker for mortality. Also found a low platelet nadir and large drop in platelet count to predict poor outcomes.

Paniccia R, Priora R, Liotta AA, Abbate R. Platelet function tests: a comparative review. Vasc Health Risk Manag. 2015;11:133–148.

A comparative review describing current test available for assessment of platelet function with focus on modern, clinically relevant tests. Describes testing methodology and clinical applications as well.

Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NKJ. Effect of thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Crit Care. 2014;18.

Systematic review evaluating TEG and ROTEM in diagnosing early coagulopathies, guiding blood transfusion and reducing mortality. Review included 55 trials and determined TEG/ROTEM are capable of diagnosing early coagulopathies in trauma.

Holcomb JB , et al. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. Ann Surg. 2012;256:476–486.

Study comparing reliability of TEG in predicting blood component transfusion when compared to CCTs in major trauma. The authors found TEG to be superior and more expedient results for transfusion component prediction.

Strauss R , et al. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med. 2002;30:1765–1771.

Prospective observational studies measuring risk factors, prevalence and outcomes of thrombocytopenic patients in medical ICUs. Identified predictors of thrombocytopenia (DIC, organ failure at presentation, CPR) and determined thrombocytopenic patients are at higher risk of bleeding with increased transfusion requirements.

Sprügel MI , et al. Antiplatelet therapy in primary spontaneous and oral anticoagulation-associated intracerebral hemorrhage. Stroke. 2018;49:2621–2629.

Study using pooled data from retrospective cohort studies and prospective single-center studies to determine the influence of concomitant antiplatelet therapy on hematoma

characteristics and outcome in ICH. Results significant for anti-platelet therapy being associated with increased ICH volume and worse functional outcomes.
Baharoglu MI , et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet. 2016;387:2605–2613.
Randomized trial investigating effect of platelet transfusion on mortality in patients with ICH on anti-platelet medication. Platelet transfusion in these patients increase mortality and severe adverse events during hospitalization.
Ruff CT, Giugliano RP, Antman EM. Management of bleeding with non–vitamin K antagonist oral anticoagulants in the era of specific reversal agents. Circulation. 2016;134:248–261.
Review article focusing on reversal of non-vitamin K antagonist oral anticoagulants including indications for use, side effects and mechanism of action.
Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010;363:1791–1800.
The investigators studied the frequency of thromboembolic events in 35 randomized, placebo-controlled trials of rFVIIa. Using pooled data, they determined off-label use of rFVIIa is associated with increased risk of arterial thromboembolic events.

Postoperative Bleeding

Al-Huniti A , Kahr WH . Inherited platelet disorders: diagnosis and management. Transfus Med Rev. 2020 Sep 19;S0887-7963(20):3–30052. doi: 10.1016/j.tmrv.2020.09.006. Epub ahead of print. PMID: 33082057.
This review articles describes the different platelet disorders and works through the diagnosis including history and physical exam findings, laboratory studies, and finishes with treatment strategies.
Brenner A , Afolabi A , Ahmad SM , et al.; HALT-IT trial collaborators. Tranexamic acid for acute gastrointestinal bleeding (the HALT-IT trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. Trials. 2019 Jul 30;20(1):467. doi: 10.1186/s13063-019-3561-7. PMID: 31362765; PMCID: PMC6668177.
This is an international, double blinded RCT of 12,000 patients with acute upper or lower GI bleed. Patients were randomized to either TXA or placebo. They found no difference in mortality, rebleeding, or arterial thrombotic events, but did find an increase in venous thrombosis. Based on these findings, the authors do not recommend TXA for GI bleeding.
CRASH-3 trial collaborators . Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019 Nov 9;394(10210):23–1713. doi: 10.1016/S0140-6736(19)32233-0. Epub 2019 Oct 14. Erratum in: Lancet. 2019 Nov 9;394(10210):1712. PMID: 31623894; PMCID: PMC6853170.
The follow up study to Crash-2, Crash-3 is a multi-center international RCT that enrolled >12,000 patients. It showed that early administration of TXA to TBI patients, decreased head injury related deaths in patients with mild-moderate TBI. The risk of blood clots and seizures were similar between the two groups.
Curnow J , Pasalic L , Favaloro EJ . Why do patients bleed? Surg J (N Y). 2016 Feb 24;2(1):e29–e43. doi: 10.1055/s-0036-1579657. PMID: 28824979; PMCID: PMC5553458.
This review provides an overview of reasons that patients bleed in the perioperative setting. It offers guidance on how to screen for these conditions, through appropriate patient history and examination prior to surgical intervention, as well as guidance on investigating and managing the cause of unexpected bleeding.
Dagi TF . The management of postoperative bleeding. Surg Clin North Am. 2005 Dec;85(6):213–1191, x. doi: 10.1016/j.suc.2005.10.013. PMID: 16326202.
This review article addresses the prompt diagnosis, differential, and management of postoperative bleeding.
Fahrendorff M , Oliveri RS , Johansson PI . The use of viscoelastic haemostatic assays in goal-directing treatment with allogeneic blood products – a systematic review and meta-

analysis. Scand J Trauma Resusc Emerg Med. 2017 Apr 13;25(1):39. doi: 10.1186/s13049-017-0378-9. PMID: 28403868; PMCID: PMC5390346.

This meta-analysis reviews RCTs performed on patients in hemorrhagic shock, assessing the utility of the viscoelastic hemostatic assay (VHA). The VHA groups (15 RCTs) had decreased transfusion requirements and decreases blood loss compared to the control groups.

Gonzalez E, Moore EE, Moore HB. Management of trauma-induced coagulopathy with thrombelastography. Crit Care Clin. 2017 Jan;33(1):119–34. doi: 10.1016/j.ccc.2016.09.002. PMID: 27894492; PMCID: PMC5142763.

This RCT (TXA or placebo) enrolled 12,009 patients with mixed upper and lower GI bleeds. There was no difference in the mortality rates between groups. There was no difference in arterial complications, but the rate or VTE was higher in the TXA group.

Haider MZ , Anwer F . Acquired hemophilia. 2020 Aug 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. PMID: 32809329.

This review article discusses the types of hemophilias, diagnostic tests, and treatment strategies.

Holcomb JB , Tilley BC , Baraniuk S , et al.; PROPPR Study Group. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs. A 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015 Feb 3;313(5):82–471. doi: 10.1001/jama.2015.12. PMID: 25647203; PMCID: PMC4374744.

680 patients from 12, level 1 trauma centers, were placed in a RCT that compared plasma, platelets, and red blood cells in a 1:1:1 ratio to a 1:1:2 ratio. Results did not show a significant difference in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours. Even though there was an increased use of plasma and platelets transfused in the 1:1:1 group, no other safety differences were identified between the 2 groups.

Levi M . Management of bleeding in patients treated with direct oral anticoagulants. Crit Care. 2016 Aug 20;20:249. doi: 10.1186/s13054-016-1413-3. PMID: 27543264; PMCID: PMC4992194.

This review article discusses the novel anticoagulants and their reversal agents.

Morrison JJ , Dubose JJ , Rasmussen TE , Midwinter MJ . Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. Arch Surg. 2012 Feb;147(2):3–911. doi: 10.1001/archsurg.2011.287. Epub 2011 Oct 17. PMID: 22006852.

The MATTERs study was a military follow up study after Crash-2. The study is retrospective, 896 patients were identified and 292 received TXA within 1 hour. There was a statistically significant risk reduction in mortality, when TXA was given. All patients who received TXA also received blood products and an operation. There was an increase in blood clots in the TXA group.

Roberts I , et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess. 2013;17(10):1. doi:10.3310/hta17100.

Spinella PC , Perkins JG , Grathwohl KW , Beekley AC , Holcomb JB . Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma. 2009 Apr;66(4 Suppl):S69–76. doi: 10.1097/TA.0b013e31819d85fb. PMID: 19359973; PMCID: PMC3126655.

This study retrospectively analyzed 354 patients. The two groups consisted of patients who received warm whole blood plus pRBCs and FFP and those that received pRBCs, FFP, and platelets, no whole blood. The whole blood group had a statistically significant 24 hour and 30-day survival.

WOMAN Trial Collaborators . Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017 May 27;389(10084):16–2105. doi: 10.1016/S0140-6736(17)30638-4. Epub 2017 Apr 26. Erratum in: Lancet. 2017 May 27;389(10084):2104. PMID: 28456509; PMCID: PMC5446563.

This RCT of 20,060 women who had postpartum hemorrhage, enrolled patients to receive TXA or placebo. Death due to bleeding was the only statistically significant endpoint, with a slight reduction in the TXA group. Overall mortality, risk of hysterectomy, or complications

(like VTE) were not different between the groups.

Transfusion Trigger

Carson JL , Duff A , Poses RM , et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet. 1996;348(9034):1055–1060.

A retrospective cohort study in 1958 patients undergoing surgery who refused blood transfusions that shows the natural history and perioperative consequences of anemia. The 30-day mortality was 33.3% in those with a preoperative hemoglobin <6 g/dL, as opposed to 1.3% in patients with a preoperative hemoglobin of 12 g/dL or higher. In those patients with underlying cardiovascular disease, the risk of death increased precipitously with preoperative hemoglobin levels <10 g/dL compared to those without cardiovascular disease.

Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med*. 2011;365(26):2453–2462.

The FOCUS trial is one of the largest RCTs evaluating transfusion triggers. It enrolled 2016 patients with a history of, or underlying risk factors for, cardiovascular disease undergoing surgical hip fracture repair and randomized them into a restrictive (hemoglobin <8 g/dL or symptomatic of anemia) transfusion strategy versus a liberal transfusion strategy (hemoglobin <10 g/dL). There was no difference in the primary outcome of death or the ability to walk across the room between the restrictive and liberal groups (OR 1.01, 95% CI 0.84–1.22), in-hospital death or acute coronary syndrome (4.3% vs. 5.2%), or 60-day mortality (6.6% vs. 7.6%).

Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J. 2013;165:964–971.

The MINT pilot trial enrolled 110 patients admitted for acute coronary syndrome and randomized to either a restrictive threshold group (hemoglobin <8 g/dL or symptoms of anemia) or liberal group (hemoglobin <10 g/dL). The 30-day mortality rate was lower in the liberal transfusion group when compared to the restrictive group (1.8% vs. 13%, p = 0.032). The results of this pilot trial should be interpreted cautiously since small trials need to be confirmed with larger studies.

Carson JL, Stanworth SJ, Alexander JH, et al. Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease. *Am Heart J*. 2018; 200:96–101.

This most recent systematic review is an updated one to the 2016 Cochrane review and includes a total of 37 trials and 19,049 patients, focusing on new data in patients with cardiovascular disease. The 30-day mortality in cardiac surgery was no different between restrictive and liberal transfusion strategies (RR 0.99, 95% CI 0.74–1.33). Overall, in 26 trials with 15,681 patients, there was no difference in 30-day mortality between the two strategies (RR 1.00, 95% CI 0.86–1.16).

Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion Thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev. 2021;10:CD002042.

This Cochrane database systematic review and meta-analysis summarized trials evaluating restrictive versus liberal RBC transfusion thresholds including 47 RCTs and 20,599 patients. Restrictive transfusion strategies reduced RBC transfusions by 41% (RR 0.59, 95% CI 0.53-0.66) and did not change the 30-day mortality (RR 1.0, 95% CI 0.86–1.16) when compared with liberal transfusion strategies. Updated reviews have found nearly identical results.

Hébert PC , Wells G , Blajchman MA , et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian Critical Care Trials Group [see comments]. N Engl J Med. 1999;340(6):409–417.

The TRICC trial was the first RCT evaluating transfusion thresholds utilizing a restrictive vs. liberal transfusion strategy. The trial enrolled 838 euvolemic ICU patients and found a non-significant lower 30-day mortality between the restrictive (hemoglobin <7 g/dL) and the liberal (hemoglobin <10 g/dL) transfusion groups (18.7% vs. 23.3%, p = 0.11). However, the restrictive group did have fewer cases of MI (0.7% vs. 2.9%, p = 0.02) and pulmonary edema

(5.3% vs. 10.7%, p <0.01).

Holst LB , Haase N , Wetterslev J , et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371:1381–1391.

The TRISS trial is a RCT comparing a restrictive (hemoglobin <7 g/dL) transfusion strategy vs. A liberal (hemoglobin <9 g/dL) in 998 ICU patients with septic shock. The 90-day mortality did not differ between the restrictive (43%) and liberal (45%) transfusion groups (RR 0.94, 95% CI 0.78–1.09; p = 0.44).

Murphy GJ , Pike K , Rogers CA , et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372:997–1008.

2003 cardiac surgery patients in the TITRe2 trial were randomized to a restrictive group (hemoglobin <7.5 g/dL) or a liberal group (hemoglobin <9 g/dL). The 30-day mortality did not differ between the restrictive (2.6%) and the liberal (1.9%) group, the 90-day mortality was statistically favored the liberal transfusion group (2.6% vs. 4.2%; OR 1.64, 95% CI 1.00–2.67; p = 0,045).

Mazer CD , Whitlock RP , Fergusson DA , et al. Red-cell transfusion threshold for cardiac surgery. N Engl J Med. 2017;377:2133–2144.

Mazer CD , Whitlock RP , Fergusson DA , et al. Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. N Engl J Med. 2018;379:1224–1233.

The TRICS III trial randomly allocated 5243 patients undergoing cardiac surgery to restrictive transfusion threshold of hemoglobin <7.5 g/dL and liberal threshold of hemoglobin <9.5 in OR/ICU patients and <8.5 g/dL in non-ICU patients. This trial found no differences in 28-day mortality rates between the two groups (3% in restrictive vs. 3.6% in liberal; OR 0.85, 95% CI 0.62–1.16). Six-month follow-up confirmed the short-term results.

Robertson CS , Hannay HJ , Yamal, J-M , et al. Effect of erythropoietin and transfusion threshold on neurologic recovery after traumatic brain injury: a randomized controlled trial. JAMA. 2014;312: 36–47.

The investigators used a 2 × 2 factorial design to determine if one of two transfusion strategies and administration of erythropoietin or placebo would result in improved neurologic outcome in patients with traumatic brain injury. Compared to placebo, erythropoietin had no effect on favorable outcomes. Thromboembolic events were higher in the erythropoietin group. Outcomes were similar in the two transfusion strategy groups. Adverse outcomes were higher the liberal transfusion group.

Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368(1):11–21.

This RCT enrolled 832 patients with acute upper gastrointestinal bleeding and randomized them to a restrictive strategy (hemoglobin <7 g/dL) or a liberal strategy (hemoglobin <9 g/dL). The likelihood of survival at 45 days was higher in the restrictive group when compared with the liberal group (95% vs. 91%; HR 0.55, 95% CI 0.33–0.92; p = 0.02). This trial was notable for being the first transfusion trial showing a mortality benefit using a restrictive transfusion strategy.

Landmark Article of the 21st Century

A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL of TRANSFUSION REQUIREMENTS in CRITICAL CARE

Hébert PC et al., *N Engl J Med*. 1999 FEB 11;340(6):409–417

Commentary by Paul C. Hébert

It has been 22 years since the publication of the TRICC trial [1]. Since then, 47 randomized trials of transfusion triggers have been published, all generally demonstrating that a restrictive transfusion strategy decreases red cell transfusions by 40% without any negative consequences on clinically important outcomes [2]. If anything, outcomes were better in some subgroups in the restrictive arm.

The journey started in 1991, where as a research fellow, I wondered about exploring whether a much more liberal strategy (threshold held greater than 12.0 g/dL) versus a much more restrictive one (transfusion threshold less than 7.0 g/dL) would improve oxygen delivery sufficiently to save lives of supply dependent patients with septic shock. I wrote up the study as part of a clinical trials course for my Master degree. I continued to refine the protocol over the next 2 years. Then, I presented the study at the Canadian Critical Care Trials Groups (CCCTG) in the Spring of 1993. During my presentation to Canada's leading intensivists,

every part of the trial was scrutinized and questioned.

First, the premise. My colleagues were far less interested in the concept of driving up oxygen delivery to save lives but far more interested in simply understanding how and when to transfuse red cells. They then pointed out that red cell transfusions may have important effects on immune and inflammatory responses, causing worsened organ injury and possibly increased rate of infection. Through our discussions, it became clear that both arms of the trial had its proponents, with half believe enhance oxygen transport and support for the sick heart would save lives whilst others believing that red cells had important adverse biological effects in critically ill patients. Unfortunately, it also became clear that each side was entrenched in their respective views and practices. The discussion became very animated with one side stating the other was engaged in malpractice. Then, one wise member of our group stood up to say that the divergent views in a largely data free zone were in fact exactly why we needed to do the trial. And thereafter, we had a few more hours of constructive debate. All of the trial design element were discussed and improved.

After assembling a team of critical care physicians—a world class biostatistician, Dr. George Wells, and a transfusion medicine expert, Morris Blajchman—we received a Medical Research Council grant on our first submission. And then, we implemented the project, attempting to recruit 2300 patients over the next 5 years. After 4 years, fewer patients and physicians were agreeing to participate in the study. Canadians were hearing about contaminated blood scandals on a daily basis because of an ongoing Royal Commission (equivalent to Senate hearings or investigations in the US). Despite our best efforts, we were unable to increase enrollment rates. We finally decided to close out the study after 838 patients, an insufficient number to properly ensure that both arms of the trial were equivalent.

A few months later, after all of data was in and cleaned, the trial statistician and I proceeded to go through the primary analysis together. To our surprise, the restrictive group seemed to do a bit better. I could not believe my eyes. I asked to check the coding. Could we have mislabeled the group? He said no. He had already checked. And then, I wanted to know a lot more. Were there subgroups more affected than other? Were results consistent? What about secondary outcomes? What about high risk groups, like patients with heart disease? the enthusiasm of that day is still with me. To be looking at data that no one else had seen! and especially, with results that were so unexpected. We thought we were going to find nothing in an underpowered study. Instead, we were looking at data from a study that challenged existing norms. We followed this work with several other studies to explore why red cell transfusion may have adversely affected outcomes including studies leucoreduction (JAMA papers) led by Dean Fergusson and a major Age of Blood study (ABLE) led by myself, Jacques Lacroix, Dean Fergusson and Alan Tinmouth (NEJM). With my pediatric colleague, Jacques Lacroix, Finally, Jacques Lacroix myself and others led a major pediatric critical care trials also demonstrating that a restrictive transfusion strategy decreased red cell transfusions while not increasing the rates of organ failure in children.

It then took over another decade and many other studies with similar findings before red cell transfusion practice changed. It is personally very gratifying to have been part of such an important team effort, especially as a young scientist. I am humbled by the long term impacts of our work. The drastic decrease in red cell use accompanied by few clinically important consequences is gratifying. I am most proud of the fact that we opened up a field of research where the true clinical impacts of transfusions are still being explored. It has spread well beyond critical care and red cells. I only hope our next generation considers a career in clinical research.

Hébert PC , Wells G , Blajchman MA , et al., the Canadian Critical Care Trials Group . Transfusion requirements in critical care: a multicentre randomized controlled clinical trial. N Engl J Med. 1999;340:409–417.

Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion Thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev. 2021;10:CD002042.

Massive Transfusion

Balogh Z , Mckinley BA , Cocanour CS , et al. Supranormal trauma resuscitation causes more case of abdominal compartment syndrome. Arch Surg. 2003 Jun;138(6):637–642.
This analysis compared supranormal resuscitation with normal resuscitation in 156 patients. Supranormal resuscitation was associated with increased crystalloid administration, decreased intestinal perfusion, and increased intra-abdominal hypertension, abdominal compartment syndrome, multiple organ failure, and death.
Borgman MA , Spinella PC , Perkins JG , et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007 Oct;63(4):805–813.
The authors compared three groups of patients with different plasma to RBC ratios who received massive transfusion. High plasma:RBC ratio (1:1.4) is independently associated with survival.
Cannon JW , Khan MA , Raja AS , et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2017 Mar;82(3):605–617.
Guideline published by the Eastern Association for the Surgery of Trauma using available evidence to recommend the use of massive transfusion and damage control resuscitation protocols with a high plasma and platelet to packed red blood cell ratio.
Como JJ , Dutton RP , Scalea TM , Edelman BB , Hess JR . Blood transfusion rates in the care of acute trauma. Transfusion. 2004 Jun;44(6):809–813.
The authors evaluated patterns of packed red blood cell use at a large level one trauma center over the course of 1 year. Three percent of patients received more than 10 units of packed red blood cells and received 71% of all packed red blood cells given. Most of these patients received plasma and platelets to treat coagulopathy.
Cotton BA , Reddy N , Hatch QM , et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg. 2011;254:598-605.
An analysis of 390 patients who underwent damage control laparotomy. Patients were divided into pre-damage control resuscitation and damage control resuscitation groups. Patients that underwent damage control resuscitation received less products and fluids, were less coagulopathic, and were associated with a 2.5-fold increased odds in 30-day survival.
Holcomb JB , Jenkins D , Rhee P , et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma. 2007;62:307–310.
A discussion on traumatic coagulopathy and the introduction of balanced blood component resuscitation.
Meyer DE , Cotton BA , Fox EE , et al. A comparison of resuscitation intensity and critical administration threshold in predicting early mortality among bleeding patients: a multicenter validation in 680 major transfusion patients. J Trauma Acute Care Surg. 2018;85:691–696.
A study with 680 patients from 12 trauma centers compared resuscitation intensity and critical administration threshold. Both are similar predictors of mortality in patients massively transfused and capture more patients than the traditional massive transfusion definition.
Morrison CA , Carrick MM , Norman MA , et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma. 2011:70:652–663.
A randomized controlled trial with 90 patients that compared a hypotensive resuscitation strategy to a standard resuscitation strategy. Patients with a lower mean arterial pressure received less blood products and fluids, and had decreased postoperative coagulopathy and mortality.
Savage SA , Sumislawski JJ , Zarzaur BL , Dutton WP , Croce MA , Fabian TC . The new metric to define large-volume hemorrhage: results of a prospective study of the critical administration threshold. J Trauma Acute Care Surg. 2015;78:224–230.
The authors evaluated 316 patients who received at least 1 unit of PRBC. They compared the traditional definition of massive transfusion to an alternate definition of critical administration threshold (CAT). CAT+ patients were associated with a two-fold increased risk of death. CAT utilizes rate and volume of transfusion, which allows for early identification of

injured patients at greatest risk of death.

Burns

Asmussen S , Maybauer DM , Fraser JF , et al. Extracorporeal membrane oxygenation in burn and smoke inhalation injury. *Burns* . 2013;39(3):429–435.

The authors performed a meta-analysis of six clinical studies to determine the effectiveness of ECMO at improving survival for patients who experience acute respiratory failure with burn and inhalation injury. The results suggest there is no improvement in survival for these patients (Survival rate 0.542, 95% CI 0.404–0.641). The authors note that there were only a few clinical trials, and they all had limited number of patients, so the role of ECMO in the treatment of burns remains somewhat unclear.

Chung KK , Coates EC , Smith DJ Jr , et al. Randomized controlled Evaluation of high-volume hemofiltration in adult burn patients with Septic shoCk and acUte kidnEy injury (RESCUE) Investigators. High-volume hemofiltration in adult burn patients with septic shock and acute kidney injury: a multicenter randomized controlled trial. *Crit Care*. 2017;21(1):289.

This multi-center, prospective randomized trial examined the impact of HVHF/CVVH on hemodynamic profile, organ function and overall survival in burn patients (n = 37) who developed septic shock with AKI. Vasopressor dependency index decreased significantly (p = 0.007) at 48 hours and multiple organ dysfunction syndrome score decreased at 14 days (p = 0.02) for subjects in the HVHF group. There was no difference in survival or adverse events between the two groups. It should be noted that the trial was terminated early due to slow enrollment.

Greenhalgh DG , Saffle JR , Holmes JH 4th , et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. 2007;28(6):776–790.

Authors 2007 conference to define sepsis and infection criteria in burn patients. The SIRS criteria is too non-specific to be useful in burns. Triggers for sepsis concern are at least three of the following; Temp >39° or <36.5°C, progressive tachycardia, progressive tachypnea, thrombocytopenia after day 3, hyperglycemia, or decreased enteral feeding. Authors recommend not initiating multiple organ dysfunction syndrome (MODS) assessment until after completion of initial resuscitation and scores should grade organ failure over range of values.

Greenhalgh DG . Management of burns. *N Engl J Med*. 2019;380(24):2349–2359.

Author presents an excellent overview of burn care, including immediate and long-term management strategies. Special considerations for burn patients are outlined, such as fluid resuscitation protocols (Rule of Nines, Lund-Browder chart, and the Parkland formula), the hypermetabolic state, sepsis, wound healing, and wound care.

Herndon DN , Hart DW , Wolf SE , Chinkes DL , Wolfe RR . Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. 2001;345(17):1223–1229.

This randomized trial of 25 children with severe (>40% TBSA) burns showed that β-blockade blunted the typical hypermetabolic response and muscle wasting typical of burn injuries. Administration of propranolol resulted in decreased heart rate (p <0.001) and decreased resting energy expenditure (p = 0.1). It also improved net muscle protein balance from baseline (p = 0.002) in 12 of the 13 patients in the study group.

Jeschke MG , Chinkes DL , Finnerty CC , et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008;248(3):387–401.

This large case series of 242 severely burned (>30% TBSA) pediatric patients describes the pathophysiologic changes that occurred within their patient population from triage to discharge. All demonstrated hypermetabolism with significant muscle loss (muscle protein net balance of −0.05% ± 0.007 nmol/100 mL leg/min), loss of lean body mass (−4.1% ± 1.9%; p <0.05), decreased bone mineral content (3% ± 1%), decreased bone mineral density (2 ± 1%), serum protein abnormalities (p <0.05), cardiac function abnormalities (p <0.05), and significant changes to all 17 of the serum cytokines measured in the study. The authors noted that severe burns affect the expression of acute phase proteins, result in changes to serum triglycerides levels, and have dramatic effects on several important hormonal axis (GH-IGF-I,

FTI-T4, cortisone-cortisol, insulin-glucose, PTH-osteocalcin, and sex hormones).
Kildal M , Andersson G , Fugl-Meyer AR , Lannerstam K , Gerdin B . Development of a brief version of the Burn Specific Health Scale (BSHS-B). *J Trauma*. 2001;51(4):740–746.
Authors used questionnaire data from 248 burn patients to verify validity of the brief version of the burn specific health scale (BSHS-B) as compared to the older BSHS-A. The BSHS-B is a simplified outcome scale based on 40 questions and covers seven domains of burn related disability; simple functional abilities, work, body image, interpersonal relationships, affect, heat sensitivity, and treatment regimens.
Liu HF , Zhang F , Lineaweaver WC . History and advancement of burn treatments. *Ann Plast Surg*. 2017;78(2 Suppl 1):S2–S8.
Authors review the evolution of burn care over the course of human history. Excellent descriptions of early burn care including treatments recommended by ancient Egyptians, Chinese, and Greeks.
Llanos S , Danilla S , Barraza C , et al. Effectiveness of negative pressure closure in the integration of split thickness skin grafts: a randomized, double-masked, controlled trial. *Ann Surg*. 2006;244(5):700–705.
This double blind, randomized trial of 60 burn patients who received split thickness skin grafts demonstrated the effectiveness of negative pressure closure (NPC) dressings in decreasing the area of graft loss, decrease in need for secondary procedures, and decreasing hospital stay. The median area of graft loss in the NPC group was 0.0 cm 2 versus 4.5 cm 2 in the control group (p = 0.001). The NPC group also had fewer days from grafting to discharge (8 days in NPC group vs. 12 days in controls) and was less likely to require a second coverage procedure (16% in NPC group vs. 40% in controls).
Lundy JB , Chung KK , Pamplin JC , Ainsworth CR , Jeng JC , Friedman BC . Update on Severe Burn Management for the Intensivist. *J Intensive Care Med*. 2016;31(8):499–510.
This outstanding 2016 review article focuses on advancements in critical care for burn patients. It includes details on resuscitation, inhalation injury, ventilation, sedation and analgesia, infectious disease, nutrition support, organ dysfunction, wound failure and end of life considerations.
Mellemkjaer L , Hölmich LR , Gridley G , Rabkin C , Olsen JH . Risks for skin and other cancers up to 25 years after burn injuries. *Epidemiology*. 2006;17(6):668–673.
Authors examined records of 16,903 burn patients to determine long term cancer risks associated with burn injuries. Results suggest there is no increased risk for skin or any other type of cancer in burn injuries for at least 25 years following injury.
Meller D , Pires RT , Mack RJ , et al. Amniotic membrane transplantation for acute chemical or thermal burns. *Ophthalmology*. 2000;107(5):980–990.
This early 21st century prospective case series (n = 13) demonstrated the effectiveness of amniotic membrane transplantation (AMT) in promoting re-epithelialization and preventing scar formation in acute ocular burns. AMT quickly restored corneal and conjunctival surfaces (23.7 ± 9.8 days) in cases of mild to moderate burns.
Oda J , Kasai K , Noborio M , Ueyama M , Yukioka T . Hypothermia during burn surgery and postoperative acute lung injury in extensively burned patients. *J Trauma*. 2009;66(6):1525–1530.
The authors of this case series (n = 16) demonstrated that the degree of intraoperative hypothermia during burn surgery is associated with the development of acute lung injury post-operatively as well as increased polymorphonuclear neutrophil cell counts 24 hours after surgery. The study also demonstrated that there was no significant association between the development of lung injury and blood loss during surgery, transfusions received, extent of injury or duration of surgery.
Ong YS , Samuel M , Song C . Meta-analysis of early excision of burns. *Burns*. 2006;32(2):145–150.
The authors conducted a meta-analysis of six RTCs and demonstrated a significant reduction in mortality associated with early excision and grafting, but only in patients without inhalation injury (RR 0.36, 95% CI 0.20–0.65). Early excision was also associated with shorter hospital stay and greater blood transfusion requirement.
Osler T , Glance LG , Hosmer DW . Simplified estimates of the probability of death after burn injuries: extending and updating the Baux score. *J Trauma*. 2010;68(3):690–697.

Authors present a much-needed update to the Baux score, the traditional method used to calculate percent mortality after a burn injury. While quick and simple, the Baux score tends to overpredict mortality and doesn't reflect the advances in burn care or the effects of inhalation injury. Data from 39,888 burn patients was used to recalibrate the score to more accurately reflect mortality statistics as well as account for inhalation injury. The original equation is only slightly modified to account for inhalation injury, maintaining its ease of use, but the rough score can then be used to calculate an accurate percent mortality using the revised Baux score equation.

Paratz JD , Stockton K , Paratz ED , et al. Burn resuscitation–hourly urine output versus alternative endpoints: a systematic review. *Shock*. 2014;42(4):295–306.

The authors performed a systematic review of 20 studies to determine the ideal endpoint for fluid resuscitation during early burn management. They examined studies that compared traditional measures of hourly urine output with hemodynamic monitoring and other alternative endpoints. Use of hemodynamic monitoring was associated with increased survival (RR 0.77; CI 0.42–0.85; p <0.004), but inclusion of only the randomized trials demonstrated no appreciable differences in mortality between endpoints (RR 0.72; CI 0.43–1.19; p = 0.19) suggesting that more large scale studies are needed.

Petkar KS , Dhanraj P , Kingsly PM , et al. A prospective randomized controlled trial comparing negative pressure dressing and conventional dressing methods on split-thickness skin grafts in burned patients. *Burns*. 2011;37(6):925–929.

This randomized trial of 40 split thickness skin grafts compared mean percentage of graft take in patients treated with negative pressure dressings versus conventional dressings. They found negative pressure closure was associated with higher rates of graft take, with a mean 96.7% versus 87.5% in those treated with conventional dressings (p <0.001). They also note a significant decrease in the mean days required for graft take from 11 days for those in the control group to 8 days for those treated with negative pressure dressings (p <0.001).

Joo HS, Lee SJ, Lee S-Y, Sung KY. The efficacy of negative pressure wound therapy for split-thickness skin grafts for wounds on the trunk or the neck: a randomized controlled trial. *Wounds*. 2020;32(12):334–338.

Moisidis E , Heath T , Boorer C , Ho K , Deva AK . A prospective, blinded, randomized, controlled clinical trial of topical negative pressure use in skin grafting. *Plast Reconstructr Surg*. 2004 Sep 15;114(4):917–922.

ICU Issues with Thoracic Trauma

Meredith JW, Hoth JJ. Thoracic trauma: when and how to intervene. *Surg Clin North Am*. 2007;87(1):95–118. doi:10.1016/j.suc.2006.09.014

A review of the algorithms that applies to managing thoracic trauma patients with discussion of considerations and variables that enter into the decision-making process. Also discussed various scenarios in which these treatments apply. Covers technical considerations of multiple thoracic operative procedures.

Kirkpatrick AW, Rizoli S, Ouellet J, et al. Occult pneumothoraces in critical care. *J Trauma Acute Care Surg*. 2013;74(3):747–755. doi:10.1097/ta.0b013e3182827158

Interim analysis of the Occult Pneumothoraces in Critical Care which is a unblinded, multicenter, prospective randomized control trial comparing pleural drainage to close clinical observation among trauma patients with occult pneumothorax requiring positive pressure ventilation. Discusses positive and negative outcomes of conservative management of occult pneumothorax.

Moore FO, Goslar PW, Coimbra R, et al. Blunt traumatic occult pneumothorax: is observation safe?—Results of a prospective, AAST multicenter study. J Trauma: *Injury Infect Crit Care*. 2011;70(5):1019–1025. doi:10.1097/ta.0b013e318213f727

A prospective, observational, multicenter study from 16 trauma centers over 2 years to identify patients with occult pneumothorax and discussed the possibility of conservative management. They found that observations resulted in a 6% failure rate in non-intubated

patients and a 14% failure rate in patients on positive pressure ventilation. None of the 448 patients observed progressed to tension pneumothorax.

Prakash PS, Moore SA, Rezende-Neto JB, Trpcic S, Cannon JW. Predictors of retained hemothorax in trauma: results of an Eastern Association for the Surgery of Trauma multi-institutional trial. *J Trauma Acute Care Surg*. 2020 Oct;89(4):679–685. doi: 10.1097/TA.0000000000002881. PMID: 32649619.

A prospective, observational, multi-institutional study from 17 centers within the United States and Canada of adult trauma patients diagnosed with an hemothorax over 2 years. They found that the retained hemothorax rate was 29% which was associated with larger hemothorax on presentation. They also noted that patients with a retained hemothorax had higher rates of pneumonia and longer hospital length of stay.

Gilbert RW, Fontebasso AM, Park L, Tran A, Lampron J. The management of occult hemothorax in adults with thoracic trauma: a systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2020;89(6):1225–1232.
doi:10.1097/ta.0000000000002936

A systematic review that evaluates the clinical outcomes of conservatively managed occult hemothorax. The primary outcome of this review is failure of conservative management. Six studies were included over 70 years of publications. They determined that a hemothorax of less than 300 cc can be safely managed without TT in certain situations.

Sutyak JP, Wohltmann CD, Larson J. Pulmonary contusions and critical care management in thoracic trauma. *Thorac Surg Clin*. 2007;17(1):11–23. doi:10.1016/j.thorsurg.2007.02.001

An in-depth discussion of the pathophysiology of pulmonary contusions, current ventilator strategies and methods to combat morbidities associated with pulmonary contusions including ventilator associated pneumonia.

Brasel KJ, Moore EE, Albrecht RA, et al. Western Trauma Association critical decisions in trauma: management of rib fractures. *J Trauma Acute Care Surg*. 2017;82(1):200–203. doi:10.1097/ta.0000000000001301

Multiple management algorithms from the Western Trauma Association addressing the management of adult patients with rib fractures. This paper discusses work up, pain control options, operative and non-operative treatments, and follow-up recommendations.

Simon B, Ebert J, Bokhari F, et al. Management of pulmonary contusion and flail chest: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73(5):S351–S361. doi:10.1097/ta.0b013e31827019fd

The Eastern Association for the Surgery of Trauma (EAST) practice management guidelines for patients with pulmonary contusions and flail chest. There are multiple level 2 and 3 recommendations made for diagnosis and treatments of pulmonary contusions and flail chest. They also discuss the historical treatments and discuss how these have evolved over time.

Walkey AJ, Nair S, Papadopoulos S, Agarwal S, Reardon CC. Use of airway pressure release ventilation is associated with a reduced incidence of ventilator-associated pneumonia in patients with pulmonary contusion. *J Trauma: Injury Infect Crit Care*. 2011;70(3). doi:10.1097/ta.0b013e3181d9f612

A retrospective cohort study looking at 68 patients treated with airway pressure release ventilation (APRV) for pulmonary contusions. They found that APRV when used in treatment of pulmonary contusions is associated with a decrease in ventilator associated pneumonia. They also noted that APRV was not associated with increased hospital mortality or change in ventilator days.

Pieracci FM, Leasia K, Bauman Z, et al. a multicenter, prospective, controlled clinical trial of surgical stabilization of rib fractures in patients with severe, nonflail fracture patterns (Chest Wall Injury Society NONFLAIL). *J Trauma Acute Care Surg*. 2020 Feb;88(2):249–257. doi: 10.1097/TA.0000000000002559. PMID: 31804414.

A multicenter, prospective, controlled, clinical trial over 12 centers comparing surgical rib fixation within 72 hours to medical management. They found that patients who underwent surgical rib fixation early had better quality of life, decreased narcotic consumption, and decreased pleural space complications than the medical management group.

Cheng D, Mcnickle AG, Fraser DR, et al. Early characteristics and progression of blunt traumatic aortic injuries at a single level I trauma center. *Vasc Endovasc Surg*.

2021;55(2):105–111. 153857442096645. doi:10.1177/1538574420966450
A retrospective review of the University Medical Center of Southern Nevada trauma registry of 32 patients with blunt aortic injury managed either operatively or non-operatively. They discussed grading systems of injury and current treatments of each grade. They note that grade 1 and 2 injury have been managed non-operatively successfully and discuss the failure rates and follow-up needed for treatment.
Karmy-Jones R, Hoffer E, Meissner MH, Nicholls S, Mattos M. Endovascular stent grafts and aortic rupture: a case series. *J Trauma*. 2003 Feb;55(5):805–10. doi: 10.1097/01.TA.0000094429.98136.29. PMID: 14608148.
Retrospective review over 6 years at a single institution describing 11 patients with thoracic aortic rupture treated with endovascular stent instead of open repair. This paper discussed the technical considerations for stent placement as well as the types of stents that lead to the most successful treatment. They also discuss pitfalls of treatment and ways to treat endoleaks or stent grafts that are not seated correctly.
Lee WA, Matsumura JS, Mitchell RS, et al. Endovascular repair of traumatic thoracic aortic injury: clinical practice guidelines of the Society for Vascular Surgery. *J Vasc Surg*. 2011;53(1):187–192. doi:10.1016/j.jvs.2010.08.027
A systematic review discussing practice guidelines for endovascular repair of thoracic aortic injury. This paper polled experts and came to a consensus on a select number of issues to guide clinical practice. They describe a grading system for injury, and discusses treatment guidelines for timing of repair, medical management of injury, current grafts available, repair related to the age of the patient, vascular access, coverage of the left subclavian artery, systemic heparinization, and placement of a spinal drain to aid in paraplegia prevention.
Rabin J, Dubose J, Sliker CW, O'Connor JV, Scalea TM, Griffith BP. Parameters for successful nonoperative management of traumatic aortic injury. *J Thorac Cardiovasc Surg*. 2014;147(1):143–150. doi:10.1016/j.jtcvs.2013.08. 053
Retrospective review of 97 patients from the University of Maryland over 4.5 years. They discuss current medical management techniques for grades 1 and 2 aortic injury as well as current surgical techniques for grades 3 and 4 injury.
Clancy K, Velopulos C, Bilaniuk JW, et al.; Eastern Association for the Surgery of Trauma. Screening for blunt cardiac injury: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012 Nov;73(5 Suppl 4):S301–S306. doi: 10.1097/TA.0b013e318270193a. PMID: 23114485.
The Eastern Association for the Surgery of Trauma (EAST) practice management guideline updates the original from 1998 recommendations on blunt cardiac injury. This guideline has multiple level 1, 2, and 3 recommendations for screening and workup of blunt cardiac injury.

ICU Issues with Abdominal and Pelvic Trauma

Coccolini F , Kobayashi L , Kluger Y , et al. Duodeno-pancreatic and extrahepatic biliary tree trauma: WSES-AAST guidelines. World J Emerg Surg. 2019;14:56. http://doi.org/10.1186/s13017-019-0278-6.
This consensus paper outlines the optimal evaluation and management of duodeno-pancreatic and extra-hepatic biliary tree trauma for both pediatric and adult populations. The recommendations are further emphasized by the sequelae of late presentation and associated increased morbidity and mortality.
Tisherman SA , Stein DM . ICU management of trauma patients. Crit Care Med. 2018;46:1991–1997.
The authors provide a concise definitive review of the initial assessment and intensive care management of critically ill trauma patients. First ventilator management, massive transfusion, and coagulopathy are addressed. Next, the authors highlight specific injuries and challenges inherent to each organ system. Finally, this paper exposes care as a continuum and the challenges of overlapping management.
McNutt MK , Chinapuvvula NR , Beckmann NM , et al. Early surgical intervention for blunt bowel injury: the Bowel Injury Prediction Score (BIPS). J Trauma Acute Care Surg.

2015;78:105–111.
The author describes a new simple score to identify blunt bowel injuries that require early surgical intervention. Retrospective analysis of 110 patients at a single center identified 3 predictors: admission CT scan grade of mesenteric injury, white blood cell count, and abdominal tenderness. A score greater than or equal to 2 strongly predicted blunt hollow viscus injury for which early surgical intervention is indicated.
Fakhry SM , Allawl A , Ferguson PL , et al. Blunt small bowel perforation (SBP): an Eastern Association for the Surgery of Trauma multicenter update 15 years later. J Trauma Acute Care Surg. 2019;86:642–650.
After reviewing 127,919 trauma admission and 94,743 activations, these authors show initial CT scans continue to miss SBP. They recommend that any intraperitoneal abnormalities on initial CT scan should indicate high suspicion and recommend repeat CT or therapeutic intervention at 8 hours if uncertainty remains.
Harmston C , War JBM , Patel A . Clinical outcomes and effect of delayed intervention in patients with hollow viscus injury due to blunt abdominal trauma: a systematic review. Eur J Trauma Emerg Surg. 2018;44:369–376.
These authors review patients with blunt hollow viscus injury who underwent early versus later surgical intervention. Overall mortality was 17%, and there was no difference in mortality between groups. The authors conclude that there is insufficient data to suggest a higher mortality when surgery is delayed 24 hours.
Swaid F , Peleg K , Alfici R , Matter I , Osha O , Ashkenazi I , Givon A , Israel Trauma Group , Kessel B . Concomitant hollow viscus injuries in patients with blunt hepatic and splenic injuries: an analysis of a National Trauma Registry database. Injury. 2014;45:1409–1412.
A retrospective cohort study of 57,130 patients with blunt torso injury. Authors show that blunt splenic and or blunt hepatic injury, particularly if combined, predicts the presence of hollow viscus injury (HVI). Isolated blunt splenic injury clearly correlates with an increased incidence of HVI, however isolated hepatic injury may not.
Jurkovich GJ . AAST invited lecture: Pancreatic trauma. J Trauma Acute Care Surg. 2019;88(1):19–24.
This author reviews pancreatic physiology, four diagnostic components of pancreatic trauma and controversies of management. During his discussion of management, he highlights variations in peripancreatic anatomy and surgical options for injuries grade III or greater.
Liu H , Yu L , Yang L , Green MS . Vasoplegic syndrome: an update on perioperative considerations. J Clin Anesth. 2017;40:63–71.
The authors review the risk factors, mechanistic pathways, clinical presentation, and management strategies of vasoplegic syndrome (VS). In addition, they suggest ways to differentiate vs from other diagnoses such as reperfusion syndrome.
Lambden S , Creagh-Brown BC , Hunt J , Summers C , Forni LG . Definitions and pathophysiology of vasoplegic shock. Crit Care. 2018;22:174.
http://doi.org/10.1186/s13054-018-2102-1
This reviews the features of VS, explores the pathophysiology and associated causes of vasoplegia. The author concludes that without a clear definition, investigation is limited.

Extremity Trauma

Hauser CJ , Adams CA Jr , Eachempati SR . Surgical infection society guideline: prophylactic antibiotic use in open fractures: an evidence-based guideline. Surg Infect (Larchmt). 2006;(74):379–405.
This study systematically reviews the effects of prophylactic antibiotic administration on the incidence of infection in complicating open fractures. As the paper states, prolonged courses of broad-spectrum antibiotics were often cited as the standard of care for prevention of infective complications at the time of its publication. Results support the conclusion that a short course of first-generation cephalosporins, begun as soon as possible after injury, significantly lowers the risk of infection when used in combination with prompt, orthopedic fracture wound management.

Higgins TF , Klatt JB , Beals TC . Lower Extremity Assessment Project (LEAP): the best available evidence on limb-threatening lower extremity trauma. Orthop Clin North Am. 2010;41(2):233–239.
This paper is a review of the Lower Extremity Assessment Project (LEAP), a prospective observational study exploring a score-based methodology in deciding whether to amputate or salvage a limb, and the various subsequent papers that leveraged the LEAP study population which explore, among other topics, long-term persistent disability, psychological distress, complications, the effects of smoking on fracture healing and complications, and the outcomes of rotational flaps vs. free tissue transfers in patients requiring flap coverage. This review highlights how the original LEAP study and subsequent papers collectively give surgeons an enhanced insight into factors that drive outcomes, and present statistics that can be used to help counsel patients at time of initial hospitalization.
Jorge-Mora A , Rodriguez-Martin J , Pretell-Mazzini J . Timing issue in open fractures debridement: a review article. Eur J Orthop Surg Traumatol. 2013;23(2):125–129.
This review article highlights several studies that discuss the impact of the timing of debridement of open fractures on the incidence of infection. The article concludes that the 14 cited studies do not establish a link between delayed surgery and infection rates, but that debridement and irrigation on the whole are important factors in reducing the prevalence of infection following an open fracture.
Townsend RN , Lheureau T , Protech J , Riemer B , Simon D . Timing fracture repair in patients with severe brain injury (Glasgow Coma Scale score <9). J Trauma. 1998 Jun;44(6):977–982; discussion 982–983.
This study evaluated all patients admitted to a level 1 trauma center over a 10 year window, who sustained a femur fracture and severe closed head injury—having a GCS score of 8 or less upon admission or during the first 8 hours after admission, and discusses the timing of operative repair of fractures and subsequent risk of secondary brain injury. The study concludes that timing of the operation was a strong predictor of operative hypotension, with 60% of the patients operated on within 2 hours experiencing hypotension. Only 1 of 12 patients (8.3%) operated on after 24 hours experienced episodes of hypotension. Eighty-nine percent of patients with severe head injury and femur fractures who had no abdominal or pelvic injuries were hypotensive if operated on in less than 2 hours.

Traumatic Brain Injury

Alali AS , Fowler RA, Mainprize TG, et al. Intracranial pressure monitoring in severe traumatic brain injury: Results from the American College of Surgeons Trauma Quality Improvement Program. J Neurotrauma. 2013;30(20):1737–1746. doi:10.1089/neu.2012.2802
The authors evaluated the relationship between ICP monitoring and mortality in centers participating in the American College of Surgeons Trauma Quality Improvement Program (TQIP). Data on 10,628 adults with severe TBI were derived from 155 TQIP centers from 2009–2011. The association between ICP monitoring and mortality was determined after adjusting for important confounders. Overall mortality (n = 3769) was 35%. Only 1874 (17.6%) patients underwent ICP monitoring, with a mortality of 32%. The adjusted odds ratio (OR) for mortality was 0.44 [95% confidence interval (CI), 0.31–0.63], when comparing patients with ICP monitoring to those without. The authors stratified hospitals into quartiles based on ICP monitoring utilization. Hospitals with higher rates of ICP monitoring use were associated with lower mortality: the adjusted OR of death was 0.52 (95% CI, 0.35–0.78) in the quartile of hospitals with highest use, compared to the lowest. The authors concluded that ICP monitoring utilization was associated with lower mortality and variability in ICP monitoring rates contributed only modestly to variability in institutional mortality rates.
Carney N , Totten AM , O'Reilly C , et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017;80(1) :5–61. doi: 10.1227/NEU.0000000000001432. PMID: 27654000.
This is the most recent Brain Trauma Foundation effort to synthesize the available evidence and to translate it into recommendations. The authors only make recommendations when

there is evidence to support them and they do not necessarily constitute complete protocols for clinical use. They intended that their recommendations be used by others to develop specific treatment protocols. These current evidence-based recommendations are grouped into three areas: treatments, monitoring and thresholds. Treatments include: decompressive craniectomy, prophylactic hypothermia, hyperosmolar therapy, cerebral spinal fluid drainage, ventilation therapies, anesthetics analgesics and sedatives, steroids, nutrition, infection prophylaxis, deep vein thrombosis prophylaxis, and seizure prophylaxis. The area on monitoring includes monitoring of intracranial pressure, cerebral perfusion pressure, and advanced cerebral monitoring. The section on thresholds talks about blood pressures, intracranial pressure, swivel perfusion pressure, and advanced cerebral monitoring.

With regard to intracranial pressure monitoring, they recommended management of severe traumatic brain injury patients using information from ICP monitoring to reduce 2-week post injury mortality. They also recommend that intracranial pressure monitoring should be used in all salvageable patients with severe traumatic brain injury and also recommend that ICP monitoring is indicated in patients with severe TBI with a normal CT scan if two or more of the following features are noted on admission: age over 40, unilateral or bilateral motor posturing, or systolic blood pressure at less than 90.

Details of these guidelines can be found at: https://www.braintrauma.org/coma/guidelines

Farahvar A , Gerber LM , Chiu Y , Carney N , Härtl R, Ghajar J . Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. J Neurosurg. 2012;117(4):729–734. Retrieved Nov 26, 2020, from https://thejns.org/view/journals/j-neurosurg/117/4/article-p729.xml

This study uses a large, prospectively collected database containing information on patients admitted to one of 20 level I and two level II trauma centers, part of a New York State quality improvement program administered by the Brain Trauma Foundation between 2000 and 2009. The authors examined the effect on 2-week mortality of ICP reduction therapies administered to patients with severe TBI treated either with or without an ICP monitor. The study population included 2134 patients with severe TBI (Glasgow Coma Scale [GCS] Score <9), 1446 patients were treated with ICP-lowering therapies; 1202 had an ICP monitor placed. They found that age, initial GCS score, hypotension, and CT scan findings were associated with 2-week mortality. They also found that patients of all ages treated with an ICP monitor in place had lower mortality at 2 weeks ($p = 0.02$) than those treated without an ICP monitor, after adjusting for parameters that independently affect mortality. They concluded that in patients with severe TBI treated for intracranial hypertension, the use of an ICP monitor is associated with significantly lower mortality.

Gerber LM , Chiu Y , Carney N , Härtl R, Ghajar J . Marked reduction in mortality in patients with severe traumatic brain injury. J Neurosurg. 2013;119(6):1583–1590. Retrieved Nov 27, 2020, from https://thejns.org/view/journals/j-neurosurg/119/6/article-p1583.xml

The authors conducted a retrospective database review and analyzed 2-week mortality due to severe traumatic brain injury (TBI) from 2001 through 2009 in New York State and examined the trends in adherence to the guidelines. Univariate and multivariate logistic regression analyses were performed to evaluate the effect of time period on case fatality. From 2001 to 2009, the case-fatality rate decreased from 22% to 13% ($p <0.0001$) and remained significant after adjusting for factors that independently predict mortality. During the time period studied, adherence to the guidelines increased and use of ICP monitoring increased from 56% to 75% ($p <0.0001$). Adherence to cerebral perfusion pressure treatment thresholds increased from 15% to 48% ($p <0.0001$). The proportion of patients having an ICP elevation greater than 25 mmHg dropped from 42% to 29% ($p = 0.0001$). Based on the author's findings they suggested a causal relationship between adherence to the evidence based guidelines and improved outcomes as represented by decreased 2-week mortality.

Kostić A , Stefanović I , Novak V , Veselinović D , Ivanov G , Veselinović A . Prognostic significance of intracranial pressure monitoring and intracranial hypertension in severe brain trauma patients. Med Pregl. 2011;64(9–10):461–465. PMID: 22097111.

This is a small Serbian prospective randomized clinical trial that looked at the prognostic value of intracranial pressure monitoring and intracranial pressure-oriented therapy in severe traumatic brain injured patients. Thirty-two patients were randomized to undergo intracranial pressure monitoring while 29 patients were managed without ICP monitoring. In the intracranial pressure monitoring group, mortality was 47% while in the other group mortality

was 66%. Because of the small sample size these large differences did not meet statistical significance. They did find however, that in the group of patients who died, there was an average intracranial pressure of 27 mm Hg compared to an intracranial pressure of 18 in the survival group and these findings were statistically significant. Based on their results these authors recommended instituting intracranial pressure-oriented therapy at 18 mm Hg after 2 hours of monitoring.

Lane PL , Skoretz TG , Doig G , Girotti MJ . Intracranial pressure monitoring and outcomes after traumatic brain injury. Can J Surg. 2000;43(6):442–448.

This is an early large retrospective Canadian registry study that looked at differences between traumatic brain injured patients treated using ICP monitors and those treated without ICP monitors over a 6-year period. The population included cases with an Injury Severity Score (ISS) greater than 12 from the 14 trauma centers in Ontario. Cases with a Maximum Abbreviated Injury Scale score in the head region (MAIS head) greater than 3 were selected for further analysis. Logistic regression analyses were conducted to investigate the relationship between ICP and death. Of the 5507 identified, 541 had an ICP monitor inserted. Their average ISS was 33.4 and 71.7% survived. Multivariate analyses controlling for MAIS head, ISS and injury mechanism indicated that ICP monitoring was associated with significantly improved survival (p <0.015). This finding strongly supports the need for a prospective randomized trial of management protocols, including ICP monitoring, in patients with severe TBI.

Mauritz W , Steltzer H , Bauer P , Dolanski-Aghamanoukjan L, Metnitz P . Monitoring of intracranial pressure in patients with severe traumatic brain injury: an Austrian prospective multicenter study. Intensive Care Med. 2008;34(7):1208–1215. doi: 10.1007/s00134-008-1079-7. Epub 2008 Mar 26. PMID: 18365169.

This is an Austrian multicenter prospective cohort study. The authors looked at 88,274 patients admitted to 32 medical/surgical and mixed Austrian ICU's between 1998 and 2004. The authors were looking at reasons why patients either received or did not receive intracranial pressure monitoring and identified factors influencing hospital mortality after TBI. The study found 1856 patients (2.1% of all ICU admissions) with severe TBI (GCS <9). Of these, 1031 (56%) received intercranial pressure monitoring. They found that younger patients, female patients, and patients with isolated traumatic brain injuries were more likely to receive intracranial pressure monitoring. Interestingly, they found that patients in medium sized centers were more likely to receive intracranial pressure monitoring and those patients in large centers. The authors concluded that ICP monitoring may possibly have beneficial effects on outcomes and they also concluded that patients with severe traumatic brain injuries should be admitted to experience centers with high patient volumes since based on their data this seem to improve outcomes.

Cremer OL , van Dijk GW , van Wensen E , et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. Crit Care Med. 2005;33:2207–2213.

This is a retrospective cohort study perform at two level I trauma centers in the Netherlands on 333 brain injured patients. Allocation was determined by which center the patients were admitted. In one center, mean arterial pressure was maintained at approximately 90 mm Hg in therapeutic interventions, based on clinical observations in CT findings. At the other center, management was aimed at maintaining ICP less than 20 any CPP greater than 70. Their primary outcome measure was an extended Glascow Outcome Score after 12 months. Only 67% of the patients in the ICP center had an intracranial pressure monitor placed. No difference was found between groups for functional outcome or in hospital mortality.

Shafi S , Diaz-Arrastia R , Madden C , Gentilello L . Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. J Trauma. 2008;64(2):335–340. doi: 10.1097/TA.0b013e31815dd017. PMID: 18301195.

This study used the National Trauma Data Bank (1994-2001) and looked at patients with blunt TBI, head-abbreviated injury score (AIS) 3 to 6, age 20 to 50 years, GCS </=8, abnormal brain computed tomographic scan, and intensive care unit admission for 3 days or more. Early deaths (<48 hours) and delayed admissions (>24 hours after injury) were excluded. They identified 708 patients who underwent ICP monitoring and 938 who did not. Multivariate logistic regression was used to determine the relationship between ICP monitoring and survival while controlling for overall injury severity, TBI severity, craniotomy,

associated injuries, comorbidities, and complications. Only 43% of patient meeting BTF criteria had ICP monitoring. After adjusting for admission GCS, age, blood pressure, head AIS, and injury severity score (ISS), ICP monitoring was associated with a reduction in survival (OR = 0.55; 95% CI, 0.39–0.76; p <0.001). The study did not address management in response to elevated intra cranial pressure or the brain specific treatments received by patients in each group.

Talving P , Karamanos E , Teixeira P , et al. Intracranial pressure monitoring in severe head injury: Compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. J Neurosurg. 2013;119(5): 1248–1254. Retrieved Nov 26, 2020, from https://thejns.org/view/journals/j-neurosurg/119/5/article-p1248.xml

This study assessed compliance with the Brain Trauma Foundation's Guidelines for the Management of Severe Traumatic Brain Injury and the effect on outcomes. This is a prospective, observational study including patients with severe blunt TBI (Glasgow Coma Scale score ≤8, head Abbreviated Injury Scale score ≥3) between January 2010 and December 2011. The study population was stratified into two study groups: ICP monitoring and no ICP monitoring. Primary outcomes included compliance with BTF guidelines, overall in-hospital mortality, and mortality due to brain herniation. Multiple regression analysis was used to determine the effect of ICP monitoring on outcomes. A total of 216 patients met the BTF guideline criteria for ICP monitoring. Compliance with BTF guidelines was 46.8%. Hypotension, coagulopathy, and older age were negatively associated with the placement of ICP monitoring devices. In-hospital mortality was significantly higher in patients who did not undergo ICP monitoring (53.9% vs. 32.7%, adjusted p = 0.019). Mortality due to brain herniation was significantly higher for the group not undergoing ICP monitoring (21.7% vs. 12.9%, adjusted p = 0.046). The authors concluded that patients managed according to the BTF ICP guidelines experienced significantly improved survival.

Chesnut R . A trial of intracranial-pressure monitoring in traumatic brain injury. *New Engl J Med* . 2012;367:2471–2481.

Pressure Wounds

Levine, JM . 100 years of bedsores: How much have we learned? Adv Skin Wound Care. 2018;31(3):139–140.

https://doi.org/10.1097/01.ASW.0000530066.59878.2b

The commentary describes the history, risks, and treatment of bed sores and the reality that we still have a long way to go to address the issues that remain around prevention, resource allocation and interdisciplinary collaboration.

European Pressure Ulcer Advisory Panel; National Pressure Injury Advisory Panel: Pan Pacific Pressure Injury Alliance . *Prevention and Treatment of Pressure Ulcers/Injuries: Clinical Practice Guideline.* 3rd ed. The International Guideline; 2019.

This international and interprofessional guideline provides up-to-date information related to pressure injury classification, injury pathways, and staging. The guideline also provides an evidenced-based review of current prevention and treatment interventions appropriate for use in various populations.

Padula W , Pronovost P , Makic, M , et al. Value of hospital resources for effective pressure injury prevention: a cost-effectiveness analysis. BMJ Qual Saf 2019;28(2):132–141.

https://dol.org/10.1136/bmjqs-2017-007505

The authors performed a cost-utility analysis using Markov modeling to evaluate 34,787 patient records. The analysis suggests that pressure injury prevention for all inpatients is cost effective and hospitals should invest in compliance with international prevention guidelines.

Padula W , Delarmente B . The national cost of hospital-acquired pressure injuries in the United States. Int Wound J. 634–640.

https://dol.org/10.1111/iwj.13071

The authors used a Markov model to simulate the accumulation of costs (in 2016 dollars) attributed to treating patients with hospital acquired pressure injuries and estimated the incremental cost of treating a HAPI at about $10,708 per patient and suggests that the

national cost attributable to HAPIs could be approximately $26.8 billion dollars. Costs are disproportionately attributable to Stage 3 and Stage 4 full-thickness wounds.

Labeau S , Alfonso E , Benbenishty J , et al. Prevalence, associated factors and outcomes of pressure injuries in adult intensive care unit patients: the DecubICUs study. Intensive Care Med. 2020;47(2):160–169.
https://doi.org/10.1007/s00134-020-0634-9

The authors of the international DecubICUs study examined data from 13,254 patients in 1117 ICUs from 90 countries. There were 6747 pressure injuries of which 3997 or 59.2% were hospital acquired and overall prevalence was 26.6%. Sacrum and heels were most common sites.

Coyer F, Cook L, Doubrovsky A, Campbell J, Vann A, McNamara G. Understanding contextual barriers and enablers to pressure injury prevention practice in an Australian intensive care unit: an exploratory study. Aust Crit Care. 2019;32(2):122–130.
https://doi.org/10.1016/j.aucc.2018.02.008

The authors describe the results of the first phase of a multiphase project (SUSTAIN study), whereby a descriptive cross-sectional cohort survey of attitudes, barriers, and enablers of pressure injury prevention was completed by 204 nurses. Subjects identified high patient acuity as a significant barrier to pressure injury prevention.

Jackson D, Sarki A, Betteridge R, Brooke J. Medical device-related pressure ulcers: a systematic review and meta-analysis. Int J Nurs Stud. 2019;92:109–120.
https://doi.org/10.1016/j.ijnurstu.2019.02.006

The authors reviewed observational studies reporting medical device-related pressure injuries. Meta-analysis of the final 29 studies was used to calculate the estimated pooled incidence and prevalence. The medical device related results demonstrated as estimated pooled incidence of 12% (95% CI 8–18) and 10% prevalence (95% CI 6–16). The results were reported with caution due to the heterogeneity observed between the studies. Common devices included respiratory devices, cervical collars, tubing devices, splints, and intravenous catheters.

Pickham D , Berte N , Pihulic M , Valdez A , Mayer B , Desai M. Effect of a wearable patient sensor on care delivery for preventing pressure injuries in acutely ill adults: a pragmatic randomized clinical trial (LS-HAPI study). Int J Nurs Stud. 2018;80:12–19.
https://doi.org/10.1016/j.ijnurstu.2017.12.012

The authors evaluated the clinical effectiveness of a wearable patient sensor to improve compliance with turning in a randomized sample of 1312 patients in two adult intensive care units. Results support the use of the sensor to improve turning compliance and reduced incidence of HAPIs.

Koerner S, Adams D, Harper S, Black J, Langemo D. Use of thermal imaging to identify deep-tissue pressure injury on admission reduces clinical and financial burden of hospital-acquired pressure injuries. Adv Skin Wound Care. 2019;32(7):312–320.
https://doi.org/10.1097/01.ASW.0000559613.83195.f9

This study included 114 consecutive adult ICU patients who received a thermal imaging and clinical assessment of areas known to be high risk for deep tissue injury (heels, sacrum, and coccyx) upon admission. The thermal assessment was performed using an FDA approved long-wave infrared thermography scanning device. Of the 308 anatomical areas of interest scanned in 114 patients, 12 thermal anomalies were identified in 9 unique patients that were consistent with nonvisual signs of DTIPIs on admission. Once identified, the patients were started on therapeutic interventions known to mitigate DTI. The majority of the anomalies (9 of 12) were found on a heel. Two of the 12 anomalies manifested as a DTI. Based on historical incidence, five would have been predicted to occur. Prevention efforts initiated based on the thermal assessment reduced the DTI rate.

Gefen A, Alves P, Creehan S, Call E, Santamaria N. Computer modeling of prophylactic dressings: an indispensable guide for healthcare professionals, Adv Skin Wound Care. 2019;32(7S):S4–S13. https://doi.org/10.1097/01.ASW.0000558695.68304.41

The authors reviewed the published literature to date employing computer finite element modeling for efficacy research of prophylactic dressings related to pressure injury development. Computer models inform the process of engineering prophylactic dressings and may be useful to provide guidance for clinical use.

ICU Monitoring

Gershengorn HB , Wunsch H , Scales DC , Zarychanski R , Rubenfeld G , Garland A. Association between arterial catheter use and hospital mortality in intensive care units. JAMA Intern Med. 2014;174(11):1746–1754.

Retrospective propensity-matched cohort analysis of over 13,000 patients with an arterial catheter in the ICU across more than 100 hospitals. There was no association between arterial catheter use and hospital mortality. In a subgroup that was receiving vasopressors the use of an arterial catheter was associated with an increased odd of death (OR, 1.08; 95% CI 1.02–1.14).

Cleverley K , Mousavi N , Stronger L , et al. The impact of telemetry on survival of in-hospital cardiac arrests in non-critical care patients. Resuscitation. 2013;84(7):878–882.

Retrospective review of 668 cardiac arrests across six hospitals within the same health system. Patients on telemetry versus no telemetry had higher survival rates both immediately following arrest (66% vs. 34%, OR = 3.67, p = 0.02) and to hospital discharge (30% vs. 6%, OR = 7.17, p = 0.01). This effect was especially present for those with asystole or ventricular fibrillation.

Jubran A. Pulse oximetry. Crit Care. 2015;19:272.

This is a general review on the technology of pulse oximetry. It reviews the principles and mechanisms behind the technology. It reviews the data showing the accuracy of the SpO2 relative to the SaO2. It reviews trials that have investigated a benefit to outcomes from the use of pulse oximetry and the lack of shown benefit.

KJ Ruskin and D. Hueske-Kraus Alarm fatigue: Impact on patient safety. *Curr Opin Anaesthesiol* . 2015;28:685–690

Review paper on prevalence and dangers of false medical alarms and alarm fatigue. Healthcare professionals may be exposed to as many as 1000 false alarms per shift. The US Food and Drug Administration has reported over 500 deaths related to false alarms over a period of 5 years.

Swan HJ , Ganz W , Forrester J , Marcus H , Diamond G , Chonette D. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. N Engl J Med. 1970;283(9):447–451.

Initial description of the PAC. Discusses design and construction of the catheter. Discusses technique for placement and gives placement data for 100 passes in 70 patients. Describes waveforms obtained by catheter.

Gore JM , Goldberg RJ , Spodick DH , Alpert JS , Dalen JE. A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocardial infarction. Chest. 1987;92(4):721–727.

Population based observational study across multiple hospitals in a single metro area. 3000 patients with acute myocardial infarction were assessed from 3-year time points across a 12-year period. Incidence of PAC use was assessed and was shown to be increasing over the 12-year period. Use of the PAC was associated with increased mortality and increased length of stay, though as this was observational it is difficult to say if this is simply because the patients that received a PAC were more ill.

Connors AF , Speroff T , Dawson NV , et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA. 1996;276(11):889–897.

Prospective cohort study looking at outcomes associated with PAC use in general ICU patients. Over 5700 patients across five hospitals over a 5-year period were observed. The use of a PAC was associated with an increased 30-day mortality (odds ratio 1.24; 1.03–1.49). Use of the PAC was also associated with increased mean hospital stay cost and increased ICU length of stay. Authors conclude these results justify a randomized controlled trial for use of the PAC.

Harvey S , Harrison DA , Singer M , et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet. 2005;366(9484):472–477.

Randomized controlled trial with over 1000 patients across 65 ICUs in the UK. See text above for further details regarding trial.

Gershengorn HB , Wunsch H. Understanding changes in established practice: pulmonary artery catheter use in critically ill patients. Crit Care Med. 2013;41(12):2667–2676.

Retrospective cohort study assessing use of PAC from 2001–2008 across ICUs that participated with Project IMPACT database. Total PAC use decreased from 10.8% of patients to 6.2% during this time period.

Guyatt G. A randomized control trial of right-heart catheterization in critically ill patients. Ontario Intensive Care Study Group. J Intensive Care Med. 1991;6(2):91–95.

This was an attempt at a randomized controlled trial for PAC use. Only able to enroll 33 patients. There were 52 otherwise eligible patients that were excluded from enrollment as the attending physician felt that use of the PAC was ethically mandated. Not enough equipoise to complete trial.

Wiener RS , Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. JAMA. 2007;298(4):423–429.

Retrospective observational trial assessing use of the PAC between 1993–2004 across ICUs in nine different states. Rates of PAC utilization were steady between 1993–1995 and then beginning in 1996 (after Connors, et al. trial) the use began to decrease. Overall, use of the PAC decreased about 65% from 1996–2004.

Rhodes A , Cusack RJ , Newman PJ , Grounds RM , Bennett ED. A randomised, controlled trial of the pulmonary artery catheter in critically ill patients. Intensive Care Med. 2002;28(3):256–264.

Pilot single-center, randomized control trial with goal to enroll 200 patients to allow further power calculations. Enrolled 201 patients to management with either a PAC or without a PAC. Found no difference between groups in 28 day mortality. The PAC treatment group received more fluids and had increased renal failure.

Richard C , Warszawski J , Anguel N , et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2003;290(20):2713–2720.

Multicenter, randomized trial across 36 ICUs in France. Enrolled 676 patients to receive treatment either with PAC or without PAC. No difference between groups in 28 day mortality, organ failure, hospital length of stay, mechanical ventilation use, or use of vasoactive agents.

Thiele RH , Bartels K , Gan TJ. Cardiac output monitoring: a contemporary assessment and review. Crit Care Med. 2015;43(1):177–185.

This paper reviews various technologies available to make non-invasive assessments of cardiac output. It gives a review of the concept behind the Fick equation and how cardiac output can be measured invasively with a PAC. It reviews the principles and clinical considerations behind several alternative non-invasive methods.

Alcohol Withdrawal

Sarff M , Gold JA. Alcohol withdrawal syndromes in the intensive care unit. Crit Care Med. 2010;38(9):S494–S501.

This is a comprehensive review of the pathophysiology, diagnostic tests, and treatment options for patients with AWS in the ICU.

Mirijello A , D'Angelo C , Ferrulli A , et al. Identification and management of alcohol withdrawal syndrome. Drugs. 2015;75(4):353–365.

This is a “Therapy in Practice” paper with the intent to educate the reader on AWS presentation, diagnosis, and treatment algorithms.

Sullivan JT , Sykora K , Schneiderman J , Naranjo CA , Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84(11):1353–1357.

This is a landmark 1989 study which revised the CIWA-A scale and provided a shortened 10-item scale for clinical quantification of the severity of AWS, the CIWA-Ar scale. This scale offers an increase in efficiency while at the same time retaining clinical usefulness, validity, and reliability, and is widely used in clinical practice.

Saitz R , Mayo-Smith MF , Roberts MS , Redmond HA , Bernard DR , Calkins DR. Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial. JAMA. 1994;272(7):519–523.

This randomized double-blind controlled trial assessed the difference between symptom-based or individualized treatment versus standing treatment on the intensity and duration of medication therapy in patients with alcohol withdrawal syndrome. The authors reported that prophylactic medication administration prolonged treatment and increased benzodiazepine administration in comparison to symptom-based treatment. Thus, establishing symptom-triggered therapy as a gold standard for managing alcohol withdrawal syndrome.

Hendey GW , Dery RA , Barnes RL , Snowden B , Mentler P . A prospective, randomized, trial of phenobarbital versus benzodiazepines for acute alcohol withdrawal. *Am J Emerg Med.* 2011;29(4):382–385.

This was a prospective study published in 2011 comparing the use of phenobarbital versus benzodiazepine in patients with alcohol withdrawal presenting to the emergency department. Forty-four patients were randomized into the study, 25 received phenobarbital and 17 received lorazepam. The researchers monitored patient's initial CIWA score, emergency room length of stay, admission rate, and 48 hour follow up CIWA score in both arms of the study. Patients in the lorazepam arm were sent home on a 5-day taper versus those in phenobarbital arm were given a 5-day placebo. The results concluded that both phenobarbital and lorazepam were similarly effective for mild to moderate alcohol withdrawal. There was no statistical difference in baseline CIWA scores, discharge scores, ED length of stay, admission, or 48-hour follow-up CIWA scores. Both medications reduced CIWA scores from baseline. With many few prospective studies on this topic, this allowed more evidence for the use of phenobarbital in alcohol withdrawal patient especially in the emergency room as an initial treatment. With the benefit of a long acting agent on board for mild or moderate alcohol withdrawal, there is a significant decrease in the amount of benzodiazepines required for treatment and eliminates the need for tapers. For more severe alcohol withdrawal patients, they may still require higher doses of phenobarbital and benzodiazepines with a taper and closer monitoring with ICU admission.

Tidwell WP , Thomas TL , Pouliot JD , Canonico AE , Webber AJ. Treatment of alcohol withdrawal syndrome: phenobarbital vs. CIWA-Ar protocol. Am J Crit Care. 2018;27(6):454–460.

This retrospective cohort study comparing the use of phenobarbital protocol versus CIWA-Ar-guided benzodiazepine protocol found that use of phenobarbital protocol decreased ICU length of stay, hospital length of stay, incidence of invasive mechanical ventilation, and use of adjunct medications. The authors concluded that phenobarbital protocol for the treatment of alcohol withdrawal was an effective alternative to the standard-of-care protocol of symptom-triggered benzodiazepine therapy.

Gold JA , Rimal B , Nolan A , Nelson LS. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. *Crit Care Med*. 2007;35(3):724–730.

A retrospective cohort study which studied the effects of escalating doses of BZD in combination with phenobarbital in severe AWS. The results found that increasing doses in comparison to standing doses decrease the need for mechanical ventilation and ICU length of stay.

Crispo AL , Daley MJ , Pepin JL , Harford PH , Brown CV. Comparison of clinical outcomes in nonintubated patients with severe alcohol withdrawal syndrome treated with continuous-infusion sedatives: dexmedetomidine versus benzodiazepines. Pharmacotherapy. 2014;34(9):910–917.

A retrospective cohort study including non-intubated patients with severe alcohol withdrawal who were administered either a continuous dexmedetomidine infusion or a continuous benzodiazepine infusion. Primary outcome was comparing the rates of severe respiratory distress requiring mechanical ventilation or occurrence of alcohol withdrawal seizures. The study found no difference in primary outcomes, however, dexmedetomidine was associated with more adverse drug events including hypotension and bradycardia. The authors observed a benzodiazepine sparing effect with the use of dexmedetomidine and recommended the use of dexmedetomidine as an adjunct.

VanderWeide LA , Foster CJ , MacLaren R , Kiser TH , Fish DN , Mueller SW. Evaluation of early dexmedetomidine addition to the standard of care for severe alcohol withdrawal in the ICU: a retrospective controlled cohort study. J Int Care Med. 2016;31(3):198–204.

A retrospective cohort study comparing benzodiazepine requirements in critically ill patients with alcohol withdrawal syndrome who received dexmedetomidine. The study found that the use of dexmedetomidine was associated with a significant decrease in the overall use of benzodiazepines in this patient cohort. The authors concluded that use of dexmedetomidine was associated with a reduction in BZD requirement when utilized as adjunctive therapy for AWS.

Ludtke KA , Stanley KS , Yount NL , Gerkin RD. Retrospective review of critically ill patients experiencing alcohol withdrawal: Dexmedetomidine versus propofol and/or lorazepam continuous infusions. Hosp Pharm. 2015;50(3):208–213.

This retrospective chart review was conducted on ICU patients with alcohol withdrawal syndrome who received treatment with a continuous infusion of dexmedetomidine, propofol, and/or lorazepam. The study compared the incidence of mechanical ventilation, length of mechanical ventilation, and ICU as well as hospital length of stay. The authors reported a decrease in endotracheal intubation, ICU stay, and hospital length of stay with the use of dexmedetomidine infusion. Small sample size and retrospective nature of the study are the biggest limitations in recommending dexmedetomidine as a sole agent for managing AWS.

Flannery AH , Adkins, AD , Cook AM. Unpeeling the evidence for the banana bag: Evidence-based recommendations for the management of alcohol-associated vitamin and electrolyte deficiencies in the ICU. Crit Care Med. 2016;44(8):1545–1552.

The authors provide an evidence based review of the electrolyte and vitamin abnormalities associated with patients with chronic alcohol use that are admitted to the ICU. The article also discusses the pathophysiology of the metabolic derangements associated with chronic alcohol use as well as the various evidence based treatment modalities. The authors suggest abandoning the banana bag and provide recommendations on appropriate replacement dosing of various vitamins and mineral in such patients.

Nutrition

Behrens S, Kozeniecki M, Knapp N, Martindale RG. Nutrition support during prone positioning: an old technique reawakened by COVID-19. Nutr Clin Pract. 2020;36(1):105–109.

This is a review of the recommendations and challenges while providing nutrition on a patient with COVID-19 during prone positioning. Recommendations are based on including small frequent meals of high protein, calorically dense foods and beverages for the patient who can have an oral diet, and coincide the feedings with supine positioning. For patients who need specialized nutrition, EN is preferred over PN if the gastrointestinal tract is functional; placement should be performed before turning, it is recommended having the head of the bed elevation at 25°; there is no indication for gastric residual volume checks, but if there are signs of intolerance, using prophylactic prokinetic might be helpful in addition to head elevation in preventing broncho-aspiration. Parental nutrition should be delayed until hospital stay is 5 to 7 days for low-risk patients, but early PN should be considered for patients who are at high nutrition risk. The authors emphasize on focusing care in clusters and strict PPE restrictions.

Casaer MP, Mesotten D, Hermans G , et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–517.

This is a prospective, randomized, controlled, parallel-group, multicenter trial, randomized one to one ratio to early or late initiation of parenteral nutrition with a total of 4640 patients. The early initiation group received 20% glucose solution on the first and second day; and on the third-day parental nutrition, with those targeted to 100% of the caloric, go through combine enteral and parenteral nutrition. The late initiation group received a 5% glucose solution, and parental nutrition was initiated on the eighth to reach the calorie goal. The primary endpoint was the duration of dependency on ICU care in the secondary endpoints where new infections duration of antibiotic therapy, inflammation, weaning from mechanical ventilation, kidney injury. There were similar rates of death in both groups; however, the proportion of patients who were discharged alive from the ICU within 8 days was higher in the

late initiation group; this group also had one day shorter in the ICU, shorter time in mechanical ventilation and renal replacement therapy. Also, they presented with less new infections. However, the acute inflammatory response was more pronounced than in the early initiation group.

Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care. 2011;15(6):R268.

In this secondary analysis of a prospective observational study in three tertiary care surgical-medical ICU, the authors developed a score using the variables that linked starvation, inflammation, nutritional status, and clinical outcome. Using recent decreased oral intake, pre-ICU stay in the hospital as candidate variables for acute starvation in history of recent weight loss and a low BMI as measures for chronic starvation; to represent inflammatory markers they chose PCT, IL-6, and CRP. The association between risk score and mortality is attenuated in patients who meet their caloric targets. That increased nutritional risk is associated with reduced mortality in high-risk patients only. They demonstrated a statistically significant relation with 28-day mortality and ventilator 3 days except for BMI.

Leyderman I, Yaroshetskiy A, Klek S. Protein requirements in critical illness: Do we really know why to give so much? J Parenter Enter Nutr. 2020;44(4):589–598.

In this comprehensive review, the authors address the question of utilizing high doses of protein (2.0–2.5 g/kg/d) for critical care patients in general. They analyze the importance of anabolic resistance, where the elderly are the only demonstrated population to benefit from higher doses of protein. Utilizing nitrogen balance as a marker or protein requirements also showed that the selected population (renal replacement therapy) benefited from high protein doses. Using isotope-labeled studies also demonstrated that doses of 1.5 g/kg/d showed the lowest levels of catabolism in most patients and just a selective population (elderly and obese) benefited from higher doses. The authors also describe possible problems in the liver and during sepsis while using high dose protein. There is enough evidence to suggest that doses of 1.5 g/kg/d are adequate for most critical care patients. There are specific populations that might need higher doses (elderly, obese, trauma, burn, RRT), yet more evidence is needed to refute or confirm this approach to the latter populations.

Martindale R, Patel JJ, Taylor B , et al. Nutrition therapy in critically ill patients with coronavirus disease (COVID-19). J Parenter Enter Nutr. 2020;44(7):1174–1184.

This paper summarizes the first attempt to standardize recommendations for critical care nutrition support in patients with COVID-19 infection. The recommendations are based on three main principles: 1) "cluster care," 2), adherence to the Centers for Disease Control and Prevention guidelines on minimizing aerosol droplet exposure, and 3) preservation of PPE use. It is recommended initiating early EN within 24 to 36 hours of admission through an orogastric or nasogastric feeding tube, starting with a low dose hypocaloric or trophic in advancing slowly over the first week to meet the energy goal of 15 to 20 kcal per kilo of actual body weight of a standard high protein polymeric iso-osmotic enter a formula. Recommendations are given about monitoring prone positioning therapy and renal replacement therapy.

McCarthy MS, Martindale RG. Immunonutrition in critical illness: what is the role? *Nutr Clin Pract.* 2018;33(3):348–358.

This publication attempts to define what immunonutrition (IMN) is, review the essential nutrients, the role in clinical illnesses, and their proposed mechanism of action. There is enough evidence to show that immunonutrition is favorable to modulate the inflammatory response to injury and infection and improve clinical outcomes. These immunonutrients include amino acids, nucleotides, and fats, specifically glutamine, arginine, omega-3 PUFA, and RNA nucleotides. The three primary targets for these metabolic-modulating nutrients are mucosal barrier function, cellular defense function, and local or systemic inflammation prevention. Multiple benefits have been mentioned in the literature, but the only robust data showing IMN's significant benefit is in patients undergoing major surgery.

McClave SA, Taylor BE, Martindale R , et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). J Parenter Enter Nutr. 2016;40(2):159–211.

These clinical guidelines are the most comprehensive nutrition guidelines presented by the ASPEN and SCCM after reviewing the evidence of each recommendation classified from high-quality grade in randomized controlled trials, and low-quality grade for observational studies, cohort, case series, and case studies. Over most of the recommendations are based on expert consensus. It is recommended to review all the aspects of nutrition assessment, how to initiate EN, dosing, monitoring tolerance and adequacy of EN, parental nutrition indications, and specific examples for different pathologies like nutrition and pulmonary failure, renal failure, hepatic failure, acupuncture Titus, and a particular subset of populations in the surgical arena obesity, chronic illness, and sepsis.

Patel JJ, Kozeniecki M, Peppard WJ, et al. Phase 3 pilot randomized controlled trial comparing early trophic enteral nutrition with “no enteral nutrition” in mechanically ventilated patients with septic shock. J Parenter Enteral Nutr. 2020;44(5):866–873.

This is a phase 3 single center pilot parallel-group randomized controlled study, aimed to compare early traffic EN with no EN in mechanically ventilated medical ICU patients with septic shock; the study was not powered to give definitive conclusions on the outcomes. Nevertheless, the early end group reached 1.2 kcal/mL formula within 16 hours while on vasopressor. The no EN group was withheld until the vasopressor support was discontinued for at least 3 hours averaging 48 hours to start. Complications in the EN group were vomiting in 20% of the cases compared to 56% and then no EN group. There was no occlusive mesenteric ischemia (NOMI) or ileus in either group; this differs from the REDOX, CALORIES, and TARGET trials, large contemporary RCTs where NOMI occurred in 0.3%, 0.9%, and 0.05%, respectively.

Telemedicine in the ICU

Kichloo A , Albosta M , Dettloff K , et al. Telemedicine, the current COVID-19 pandemic and the future: a narrative review and perspectives moving forward in the USA. Fam Med Community Health. 2020;8(3).

Moazzami B , Razavi-Khorasani N , Dooghaie Moghadam A , Farokhi E , Rezaei N. COVID-19 and telemedicine: Immediate action required for maintaining healthcare providers well-being. J Clin Virol. 2020;126:104345.

These references detail patient and provider perspectives on the role of telemedicine during the COVID-19 pandemic.

Welch BM , Harvey J , O'Connell NS , McElligott JT. Patient preferences for direct-to-consumer telemedicine services: a nationwide survey. BMC Health Serv Res. 2017;17(1):784.

This study documents current patient preferences for the convenience and safety of telemedicine- based encounters.

Lilly CM , Zubrow MT , Kempner KM , et al. Critical care telemedicine: evolution and state of the art. Crit Care Med. 2014;42(11):2429–2436.

This review documents the pre-pandemic adoption of ICU telemedicine hub and spoke model tele-ICUs.

Ward MM , Carter KD , Ullrich F , et al. Averted transfers in rural emergency departments using telemedicine: rates and costs across six networks. Telemed J E Health. 2020.

Fiscal support from the federal government was an important driver of the increased access to critical care specialist services for rural Americans provided by tele-ICUs.

Thomas EJ , Lucke JF , Wueste L , Weavind L , Patel B. Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of stay. JAMA. 2009;302(24):2671–2678.

This academic medical center study demonstrated that when telemedicine programs were implemented by administrative fiat without bedside intensivist support that improvements of outcomes were not significant.

Lilly CM , Cody S , Zhao H , et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. JAMA. 2011;305(21):2175–2183.

This landmark study found that collaborative interprofessional ICU telemedicine-supported reengineering of critical care delivery processes was associated with improved mortality and length of stay that could be accounted for by care standardization metrics.

Lilly CM , Fisher KA , Ries M , et al. A national ICU telemedicine survey: validation and results. Chest. 2012;142(1):40–47.

This study which was sponsored by the ACCP created a validated tool for assessing adult critical care processes. This made it possible to distinguish tele-ICU implementations where processes of care were changed from those with processes of care that did not change.

Lilly CM , McLaughlin JM , Zhao H , et al. A multicenter study of ICU telemedicine reengineering of adult critical care. Chest. 2014;145(3):500–507.

This multicenter study of a geographically dispersed and nationally representative cohort of institutions that implemented hub and spoke ICU telemedicine programs found the main findings of the landmark study were also present among this sample of United States ICUs. It used the validated process of care tool (reference 8) to associate larger improvements with greater changes in the targeted processes of care. This allowed identification of the process factors that may mediate ICU telemedicine-associated improvement in length of stay and mortality. It also identified substantial variation among adopting institutions with regard to factors that were amenable to modification after tele-ICU implementation.

Kahn JM , Le TQ , Barnato AE , et al. ICU telemedicine and critical care mortality: a national effectiveness study. Med Care. 2016;54(3):319–325.

This study confirmed that mortality benefits of tele-ICU programs were evident in large administrative datasets. It is particularly convincing because these effects were evident using methods that allowed admixture of patients who did not receive tele-ICU supported care to be included in the telemedicine intervention group.

Lilly CM , Motzkus CA. ICU telemedicine: Financial analyses of a complex intervention. Crit Care Med. 2017;45(9):1558–1561.

The financial benefits of ICU telemedicine programs and the benefits of leveraging them to provide logistical support are detailed over a time period that is long enough to identify durable effects. It provides insights into the macroeconomics of adult ICU care that many intensivists are not familiar with. The study quantifies the effects of increasing access to ICU care using real-time methods that reduce length of stay and increase volume. Its main finding is that the financial benefits of ICU telemedicine program implementation to the United States hub institutions greatly exceeded its costs.

Fifer S , Everett W , Adams M , Vincequere J . Critical care, critical choices the case for tele-ICUs in intensive care. New England Healthcare Institute; Massachusetts Technology Collaborative; 2010.

http://www.masstech.org/teleICU.pdf.

This study, funded by the New England Healthcare Institute, documents increased access to critical care specialty care for the patients of spoke hospitals. In addition, it documents the financial benefits. This finding was by supported independent PriceWaterhouse Cooper audits of this and the financial outcomes paper (reference 11) and acuity adjustment methods.